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Recueil Reviews

New methodologies for enantiomeric excess (*ee*) determination based on phosphorus NMR

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I Introduction

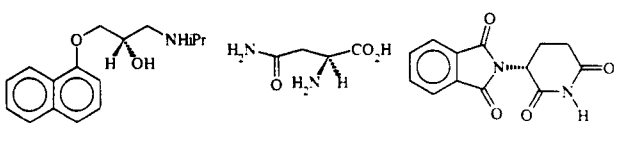
Although more than 50% of commercial drugs are chiral, less than half of these are marketed in an enantiomerically pure form[1]. Dramatic examples of the differences in pharmacological responses of enantiomers are known: (*S*)-propranolol **1** (Scheme 1) is an antihypertensive and antiarythmic used in the treatment of heart disease, whereas the *R* enantiomer acts as a contraceptive[2]. The *R* enantiomer of asparagine (**2**) tastes sweet whereas the *S* enantiomer tastes bitter. Thalidomide (**3**), commercially known as Softenon, was originally used as a racemate. Only the *R* enantiomer is responsible for the desired (sedative) therapeutic effect whereas the *S* enantiomer causes teratogenic effects[3].

Such examples are a strong incentive for the industry to market chiral compounds as single enantiomers, in response to the requirements being imposed by the regulatory authorities in Europe and the United States[4]. This resulted in a dramatic increase in research efforts towards the development of (new) chiral synthons, catalysts and procedures leading to the synthesis of enantiomerically pure products. In particular the enormous improvement in enantioselective synthesis[5] by means of stoichiometric or catalytic asymmetric transformations as well as kinetic resolution and biomimetic synthesis makes the availability of reliable analytical techniques for the correct assessment of the enantiomeric composition increasingly important.

An inherent difficulty in analyzing enantiomeric compositions is the fact that enantiomers have, apart from their chiroptical characteristics, identical physical and chemical properties (in an achiral environment)[6]. Up to the 60's, the enantiomeric purity of a chiral molecule was most frequently determined by making use of its chiroptical behaviour. This involved measuring the optical rotation of the sample under accurately defined conditions and comparing the obtained value with the known rotation of the enantiomerically pure compound, measured under the same conditions. The *optical purity* determined this manner is often equated with the *enantiomeric purity*[7], although several examples are known in which uncritical use of absolute rotations quoted in the literature led to incorrect conclusions concerning the enantiomeric excess (*ee*) of an enantioselective reaction[8,9].

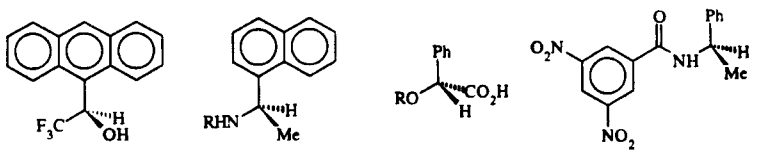
Any other method of distinguishing enantiomers must rely on the use of a chiral environment expressed by means of *diastereomer formation* or *diastereomeric interactions*. Diastereomeric interactions can be created by means of reaction with a *chiral auxiliary compound*, the use of *chiral solvating agents* or by means of *self association*. In 1967 *Raban* and *Mislow*[6b] distinguished four general approaches to determine the enantiomeric purity of a mixture of enantiomers *R* and *S*. The determination may or may not involve a separation of *R* and *S*. Furthermore, the determination may be performed on the enantiomers themselves or the enantiomers may be transformed into a pair of diastereomers *RR'* or *SR'* to facilitate the determination. Thus it follows that the determination may be carried out on enantiomers with or without separation or on diastereomers with or without separation. A further distinction can be made depending on whether the determination of the enantiomeric composition can be performed without an auxiliary probe or only in the presence of a nonracemic chiral probe. Some examples are known in which an achiral auxiliary probe is used that reacts twice with the enantiomers to give diastereomers (*vide infra*). According to these approaches several methods have been developed, although for practical enantiomeric excess determination only chromatographic and NMR methods are used extensively.

Since 1938 when *Karagunis* and *Coumoulos*[10], and independently *Henderson* and *Rule*[11], reported the first resolution of a racemic selectand on a chiral selector, liquid chromatography methods have been used to an increasing extent for enantiomeric excess determinations. This has in large measure been a result of improvements in column lifetime and performance. In 1959 *Karagunis* and *Lippold*[12] were able to separate the racemic mixtures of



(S)-1 (S)-Propanolol (S)-2 (S)-Asparagine (R)-3 (R)-Thalidomide

Scheme 1.



4 5 6 R= H, Me, Ac 7

Scheme 2.

butan-2-ol and of 2-bromobutane on optically active stationary phases making use of gas chromatographic (*GC*) methods. It took, however, seven more years before the first example of a fully reproducible separation of enantiomers by means of *GC* was reported[13]. These methods have proved to be very sensitive and widely applicable for the determination of the *ee*[14]. The enormous number of chiral selector-selectand systems developed since that time, *e.g.* by *Pirkle* and co-workers[15], made these methods probably the most powerful in the field of enantiomer separation[16]. A breakthrough in this respect was made by *Pirkle* and co-workers by the introduction of *N*-(3,5-dinitrobenzoyl)amino acids as immobilized, chiral charge-transfer-acceptor compounds used for high pressure liquid chromatography (*HPLC*)[17].

The introduction of (*R*)-2,2,2-trifluoro-1-(9-anthracenyl)-ethanol **4** as a chiral solvating agent, known as *Pirkle*'s alcohol, preceeded this methodology[18]. Chiral stationary phases based upon the ability to separate enantiomers via hydrogen bonding or via inclusion are now readily available[14,19]. In general, the chromatographic methods tend to be very fast, sensitive (often very high resolutions are obtained), precise and reproducible, making them very attractive. Moreover, chromatographic methods can be used for *ee* determination of a broad range of substrates, including *e.g.* amino alcohols, thiols and amino acids. A drawback is the necessity of (often expensive) chiral stationary phases and selection of the proper chiral column might be rather time consuming.

For the determination of the enantiomeric composition by means of NMR techniques[20] nonracemic chiral auxiliaries are needed to transform the *isochronous enantiotopic* nuclei into *anisochronous diastereotopic* nuclei[21,22]. As long as there is a large enough chemical shift nonequivalence $\Delta\delta$ (diastereomeric shift dispersion) to give baseline resolution of the appropriate signals, integration gives a direct measure of the diastereomeric composition of the sample[23]. The data can subsequently be related to the enantiomeric composition.

Three types of chiral auxiliaries are commonly used. *Chiral solvating agents* and *chiral lanthanide shift reagents* form diastereomeric complexes *in situ* that allow a direct determination of the enantiomeric composition. The use of *chiral* (or *achiral*) *derivatizing agents* requires the formation of diastereomers prior to the NMR analysis. The sample can in principle serve *as its own chiral probe*[6f,24], sometimes allowing quantification under strictly defined conditions.

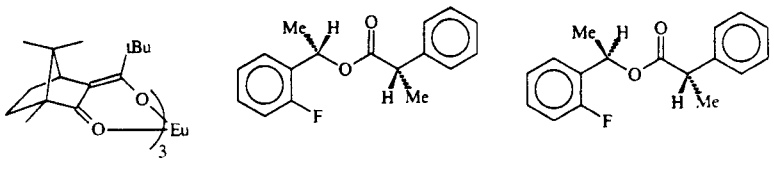
Chiral solvating agents form diastereomeric solvation complexes which solute substrate enantiomers in competition with the bulk solvent in a rapid equilibrium[25]. Detailed studies have shown that factors like temperature, concentration and the optical purity of the chiral solvating agent do not change the magnetic nonequivalence but only the magnitude[26]. Since the dissociation equilibria are relatively fast on the NMR time scale, the NMR nonequivalences are observed only in the enantiomerically enriched part of the salts. The enantiomeric composition of components in the system affects the ratio of lifetimes of bonded and nonbonded components. These changes are reflected by different $\Delta\delta$ values that vary roughly proportionally in magnitude with changes of enantiomeric purity. The advantages of this method are clear; it is quick and relatively simple to perform, and is not attended by the problems associated with kinetic resolution[27]. In Scheme 2 several other examples (**4–7**) of chiral solvating agents are given[18,25,26].

Since 1970, when *Whitesides* and *Lewis*[28] demonstrated that the application of the chiral europium complex tris[3-(1-hydroxy-2,2-dimethylpropylidene-(1*R*)-camphorato)]-europium (III) **8** (Scheme 3) resolved the externally enantiotopic methyl, methine and aromatic *ortho* protons of α-methylbenzeneethanamine, the use of chiral lanthanide shift reagents has found widespread use.

Many lanthanide shift reagents are known nowadays[29], including several water-soluble systems[108]. Although the phenomenon is not widely recognized or used, diastereomeric salts also form dynamic systems that show external diastereotopicity provided that the spectra are recorded in nonpolar solvents[26].

The use of enantiomerically pure chiral derivatizing reagents to convert enantiomers prior to the NMR analysis into a pair of diastereomers with nonequivalent external diastereotopic nuclei was first reported by *Mislow* and *Raban* in 1965[30]. They observed chemical shift non-equivalences in the ^{1}H NMR spectra of the diastereomeric α-methylbenzeneacetic esters of 2-fluoro-α-methylbenzenemethanol **9** (Scheme 3).

Determination of the *ee* using (chiral) derivatizing reagents now is the most widely used NMR technique, as the discrete diastereomers show chemical shift non-equivalences $\Delta\delta$ that are typically five times higher than for related chiral solvating agents[31]. The formation of the diastereomers must occur under strictly defined conditions that exclude racemization or kinetic resolution. When purification is necessary only methods that exclude selective enrichment of one of the diastereomers must be used. In spite of these restrictions, many chiral derivatizing reagents are known and commonly used. Some examples (**10–14**) are shown in Scheme 4.



8 9 (S,S) 9 (R,S)

Scheme 3.

The derivatizing agents contain a reactive group which can be coupled to the substrate. For example (*S*)-2-chloropropanoyl chloride **14** reacts with a large variety of nucleophiles, including alcohols, amines and unprotected amino acids. Excellent diastereomeric shift dispersions are observed in the ^{1}H NMR spectra[32]. The most widely used chiral derivatizing reagent is α-methoxy-α-(trifluoromethyl)benzeneacetic acid **10** (*MTPA*), introduced by *Mosher* in 1969[33]. It offers the possibility to use not only ^{1}H- but also ^{19}F-NMR to determine the diastereomeric composition.

Chiral derivatizing reagents often contain more than one NMR active nucleus, *e.g.* ^{19}F, ^{29}Si, ^{77}Se and ^{31}P nuclei useful for enantiomeric excess analysis[34]. It should be emphasized that chiral compounds often have a complex ^{1}H NMR spectrum with multiplets due to H-H and/or H-X coupling patterns, making analysis difficult because of overlapping signal groups. With most other NMR active nuclei, in particular ^{19}F and ^{31}P, the chemical shift dispersion is large compared to ^{1}H NMR and the nuclei are very sensitive to small structural changes in the diastereomeric adducts. When broad-band proton decoupling is used most of the spectra are simple, being a major advantage over ^{1}H NMR and allowing easy quantification of the diastereomeric signals. Since both ^{19}F and ^{31}P nuclei have an abundancy of 100%, the analysis can be performed very quickly provided the proper technical settings are used (*vide infra*)[35].

In this review several new ^{31}P NMR methods for the *ee* determination developed in our laboratories based on chiral (section II) and non-chiral (section III) phosphorus reagents, as well as related methodology, will be discussed.

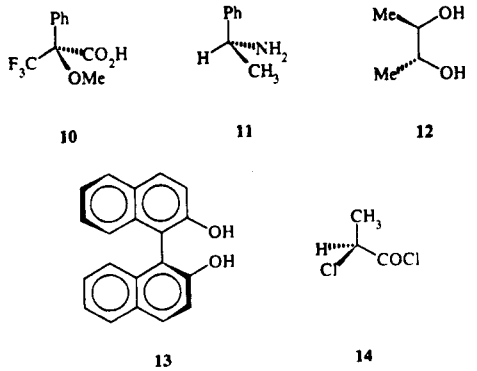
II Chiral phosphorus derivatizing reagents

The attractiveness of the phosphorus-31 nucleus for NMR analysis[35] has led to the introduction of various chiral *pentavalent* (thio)phosphoryl chlorides as derivatizing agents for chiral alcohols, amines, thiols and esters of amino acids. Derivatization proceeds by means of a displacement reaction on the phosphorus atom affording the diastereomeric products.

In order to determine the enantiomeric composition using (phosphorus) derivatizing reagents several criteria must be met:

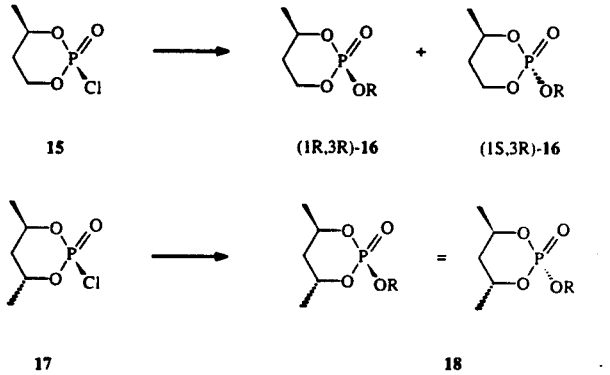
(*i*) The reagents or precursors must be available in enantiomerically pure form.

(*ii*) In the process of adduct formation reactions at (the) chiral center(s) should not occur or must be stereospecific.



10 **11** **12** **13** **14**

Scheme 4.



15 **(1R,3R)-16** **(1S,3R)-16** **17** **18**

Scheme 5.

(*iii*) The coupling reactions should proceed in high (quantitative) yield without enrichment of one diastereomer.

(*iv*) The adducts obtained must not be subjected to purification techniques, as these are a potential source for diastereomeric enrichment.

(*v*) The diastereomeric adducts must show a diastereomeric shift difference that is large enough to allow proper quantification of the selected NMR signals.

For derivatizing agents like **15** the phosphorus atom is a stereogenic as well as a chirotopic center; displacement reactions can (in principle) proceed with inversion or retention of configuration, affording the diastereomeric products (*R*)- and (*S*)-**16** as shown in Scheme 5. Although under controlled conditions normally either quantitative inversion or retention can be achieved[36], this potential complication has led to the development of several reagents possessing C_2 symmetry, for example **17** so that inversion or retention of configuration at the phosphorus center upon treatment with an enantiomerically pure substrate yields the same product **18**.

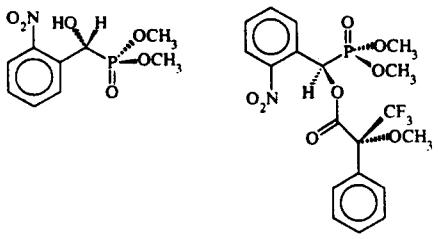
For reasons of synthetic availability, stability and desired control of stereochemistry during reaction at the phosphorus center, most of the derivatizing reagents are cyclic and based upon readily accessible chiral diols, amino alcohols or diamines that are functionalized by means of reaction with $POCl_3$ or $PSCl_3$. The reagents prepared in this way are very reactive towards a large variety of substrates. They are, however, sensitive to moisture, which restricts their use to non-aqueous solutions.

A way to circumvent the need for (thio)-phosphoryl chlorides is the use of chiral phosphonates, which upon treatment with CCl_4 and Et_3N, *in situ* afford the corresponding trichloromethyl phosphonates, which readily react with amines even in aqueous solutions.

Diastereomeric pentavalent phosphorus adducts generally show moderate diastereomeric shift differences in the decoupled ^{31}P and ^{1}H NMR, the shifts being sensitive to several factors like (im)purity of the sample, solvents (or combinations of solvents) used and the temperature.

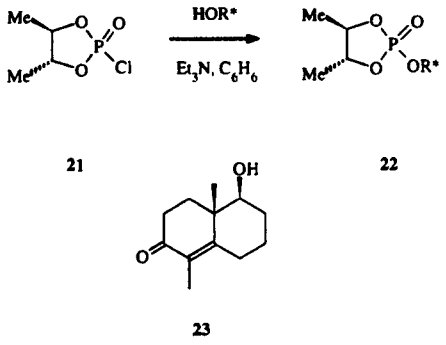
The largest diastereomeric shift differences are obtained using *trivalent* phosphorus reagents like *e.g.* phospholidines. These reagents are readily coupled to alcohols, amines and thiols, often without the need of additional reagents and allow *ee* determination using ^{1}H, ^{13}C or ^{31}P NMR. Phospholidines are, however, not suitable for derivatization in aqueous solvent systems.

Besides the preparation of covalently bonded diastereomers, several phosphorus containing compounds can also be used for the formation of diastereomeric *noncovalent associative* complexes, like *e.g.* diastereomeric salts or hydrogen bonded complexes.



19 20

Scheme 6.



21 22 23

Scheme 7.

II.A Chiral pentavalent chloro(thio)phospholane oxides as derivatizing reagents

In 1983, *Wynberg* and *Smaardijk*[37] suggested optically pure alcohol **19**, containing a phosphonate moiety, as potential reagent for the determination of the enantiomeric composition of chiral acids. It was shown that the diastereomeric shift differences by ^{31}P-NMR of adduct **20** are even larger than by ^{19}F-NMR using *Mosher*'s acid[33] (Scheme 6).

Anderson and *Shapiro*[38] introduced C_2-symmetrical chlorodioxaphospholane oxide **21** for the *ee* determination of chiral primary and secondary alcohols (Scheme 7). In the presence of base diastereomeric phosphonate esters **22** are obtained for which the diastereomeric shift dispersions were small but distinct; typically $\Delta\delta$ values are between 0 and 0.13 ppm in the ^{31}P NMR. Representative examples are given in Table I.

Reagent **21** can also be used for the analysis of *primary* alcohols, as they are prone to elimination with other derivatizing agents. Also *sterically* hindered alcohols can be analyzed using this method *e.g.* when racemic alcohol **23** is used, a diastereomeric ratio of 48:52 is found whereas the use of *Mosher*'s reagent yielded a 63:37 ratio[39]. It should be noted that anomalous reactions, like ring opening, give rise to the formation of several byproducts which, however, appear not to interfere with the actual derivatization and subsequent analysis.

Based upon earlier work of *Hall* and *Inch*[40], *Johnson* and co-workers[41] introduced chloro-1,3,2-oxazaphospholidine 2-sulfide **24** and the corresponding oxide **25**, derived from D- or L-ephedrine as chiral derivatizing reagents for chiral amines and alcohols (Scheme 8). Derivatization of chiral primary amines proceeds smoothly when triethylamine is used as a base to facilitate nucleophilic attack, whereas chiral primary and secondary alcohols are only coupled after transformation to the alkoxides using *n*-butyllithium in ether. Substitution of the halide in **24** or **25** is known to proceed with complete retention of configuration at the phosphorus center[42], although a warning for some stereochemical scrambling has been reported more recently[43].

Both the thio derivatives **26** and **27** and the oxygen analogues **28** and **29** are suitable for *ee* determination by means of ^{31}P-NMR, although the former show superior diastereomeric shift dispersions. Typical $\Delta\delta$ values are between the 0.175 ppm (D,L-α-methylbenzenemethanamine) and 0.843 ppm (D,L-4-methylpentan-2-amine) for adducts with chiral amines and 0.111 ppm and 0.301 ppm for the adducts of D,L-α-ethylbenzenemethanol and D,L-4-methyl-2-pentanol, respectively.

Diastereomeric adducts **26** and **27** can also be analyzed by means of *HPLC*, using a silica gel column and hexane/ethyl acetate as eluent. Using *HPLC*, adduct recovery is over 99.5%, indicating that the diastereomeric adducts are very robust.

Clearly, adducts **27** lead to larger diastereomeric shift differences in the ^{31}P-NMR compared with phosphonate esters **22**, which do not have a stereogenic phosphorus atom.

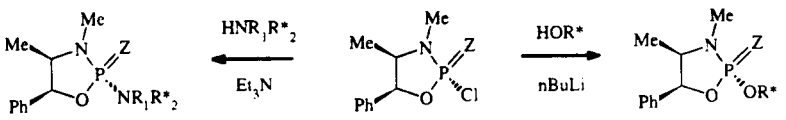
C_2-symmetrical (*S*)-1,1'-binaphthalene-2,2'-diyl phosphoryl chloride **30**, initially described as unstable by *Johnson* and co-workers[41], was reintroduced by *Kato*[44] for the *ee* determination of chiral secondary alcohols (Scheme 9).

On treatment of **30** with 1-methylimidazole and a racemic chiral alcohol, diastereomeric phosphonate esters **31** are formed, which can be analyzed by means of ^{1}H NMR, although some diastereoselectivity is observed during coupling. Surprisingly, no ^{31}P NMR data have been given for the diastereomeric products **31**. The diastereomeric shift dispersions in the ^{1}H NMR are small but distinct; typically $\Delta\delta$ values between 0.01 and 0.20 ppm are found. For racemic **32** $\Delta\delta$ values are obtained for several signals including the OAc (0.12 ppm), 10-Me (0.06 ppm) and 13-Me (0.20 ppm) moieties. Severe doubts have been expressed, however, concerning the products obtained from **30** and their subsequent analysis[41,45].

Alexakis and co-workers[46] introduced C_2-symmetrical chiral diamine based (thio)phosphoramides **33–37** (Scheme 10) as chiral derivatizing reagent for primary and se-

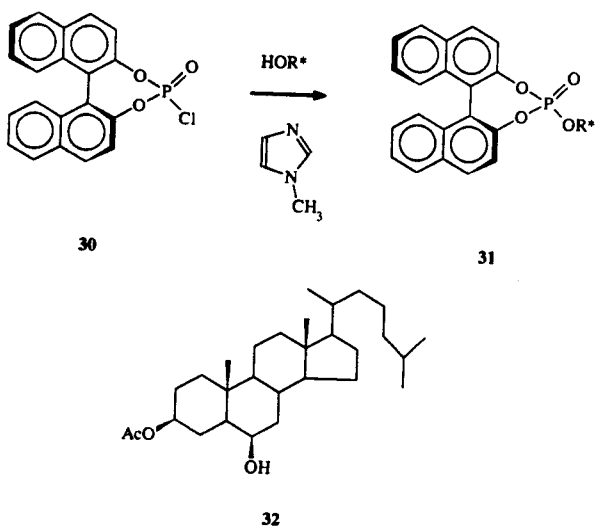
*Table I ^{31}P-NMR non-equivalences of diastereomeric products **22** obtained from reagent **21** and racemic alcohols (C_6H_6 and C_6D_6).*

D,L-Alcohols	$\Delta\delta$ (Hz)
2*O*-benzyl-3*O*-octadecylglycerol	2.40
exo-norborneol	6.11
endo-norborneol	0
butan-2-ol	0.5
meNthol	12.2
pent-1-yn-3-ol	10.13



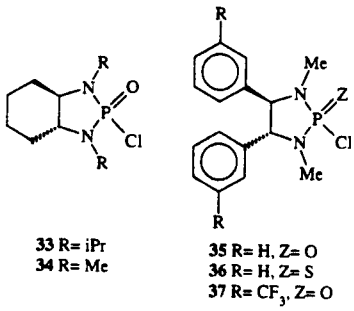
26 Z = S, **28** Z = O — **24** Z = S, **25** Z = O — **27** Z = S, **29** Z = O

Scheme 8.



30 31 32

Scheme 9.



Scheme 10.

condary chiral alcohols. The reagents are readily prepared by reaction of suitable diamines[47] with $POCl_3$ or $PSCl_3$. Like **17** these reagents possess a chirotopic non-stereogenic phosphorus atom, so that either inversion or retention of configuration at phosphorus during derivatization with an enantiomerically pure alcohol yields the same single diastereomer, as shown for **38** (Scheme 11).

Due to the reduced electrophilicity of the phosphorus atom in these reagents, associated with the presence of two P–N bonds, more forcing conditions are required in the coupling reactions with alcohols. For example, butan-2-ol does not react with **34** in THF in the presence of 2 equivalents of triethylamine, but gives several byproducts probably arising from opening of the diazaphospholane ring. The use of other bases (DMAP, DBU) or other solvents (CH_2Cl_2, DMF) does not lead to improvements. However, with the sodium alcoholates quantitative and clean conversions into the diastereomeric phosphoramidates take place. All the phosphoramidates give significant diastereomeric shift dispersion in the ^{31}P NMR (Table II), the shifts and shift differences $\Delta\delta$ being highly solvent dependent.

*Table II ^{31}P-NMR diastereomeric shift differences of products **38** obtained from racemic alcohols and reagent **34**, recorded in C_6D_6.*

D,L-Alcohol	$\Delta\delta$ (ppm)
butan-2-ol	0.269
meNthol	0.606
isomenthol	0.404
ethyl lactate	0.337
β-citronellol	0.032

The shift dispersion for diastereomeric derivatives **38** ranges from $\Delta\delta$ 0.004 ppm to 1.335 ppm. With racemic butan-2-ol, the diastereomeric shift difference is 0.269 ppm, whereas for **22** and **29** $\Delta\delta$ values are much smaller (0.006 and 0.20 ppm, respectively). So far, reagent **37** seems to be the most promising for ^{31}P NMR analysis, although unfortunately no useful diastereomeric shift differences have been obtained by ^{19}F NMR. The corresponding diamine, however, was described as an effective reagent for the analysis of chiral aldehydes[48].

In contrast to the results obtained by *Johnson*[41] and *Feringa*[93,100], thio analogue **36** induces smaller shift differences than **35**. Furthermore, because of the lower degree of polarization of the P=S bond in comparison to the P=O bond, thio amide **36** is much less reactive compared to oxygen analogue **35**; the more forcing conditions needed for reaction clearly limits the scope by preventing the analysis of sensitive substrates.

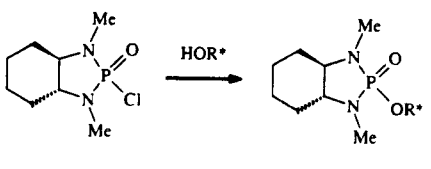
On examination of currently available methods for the *ee* determination of alcohols reagents **33–37** compare favourably, as large structural variations in substrate are allowed and sufficient diastereomeric shift dispersions are obtained. The diamines used are readily available, and can be structurally modified if desired (*vide supra*).

Dehmlow and *Sauerbier*[49] introduced phosphorylhydrazine **39** based upon L-ephedrine as a derivatizing reagent for carbonyl derivatives (Scheme 12).

Chiral ketones can form two pairs of *syn/anti* diastereomeric hydrazones **40** which can be analyzed by means of ^1H or ^{31}P NMR. Alternatively, HPLC analysis gives (only occasionally) separation of the four diastereomers and furthermore the results obtained by means of ^{31}P NMR and HPLC analysis sometimes contradict each other. Moreover, since the method is restricted to some chiral, monosubstituted cyclohexanones, its use appears to be limited.

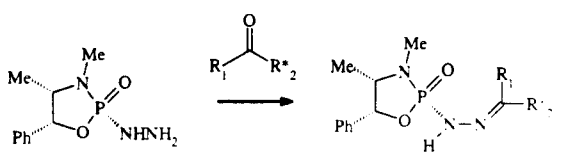
The introduction of cyclic phosphoric acids **41** as excellent resolving agents for amines, amino alcohols and amino acids by *ten Hoeve* and *Wynberg*[50], initiated the development in our laboratory of the corresponding chlorophosphorinanes **42** as a derivatizing reagents for chiral primary and secondary alcohols and amines (Scheme 13)[51].

Phosphoric acids **41** are readily obtained upon treatment of isobutyraldehyde and two equivalents of benzaldehyde with base (NaOH), followed by reaction with $POCl_3$ and basic hydrolysis affording the racemic phosphoric acids. Subsequent facile resolution[50] by means of *e.g.* L-ephedrine yields the phosphoric acids as single enantiomers, which can be transferred diastereoselectively into the air and moisture stable chlorophosphorinanes **42** by



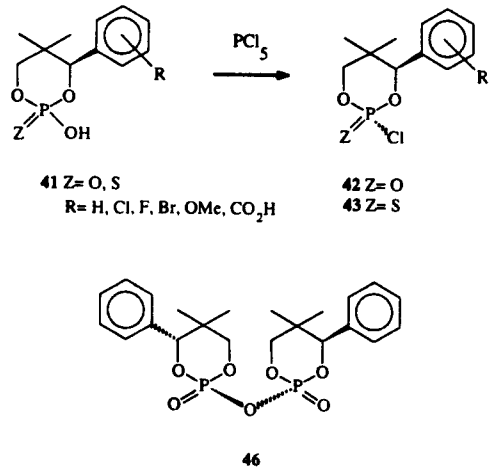
34 38

Scheme 11.



39 40

Scheme 12.



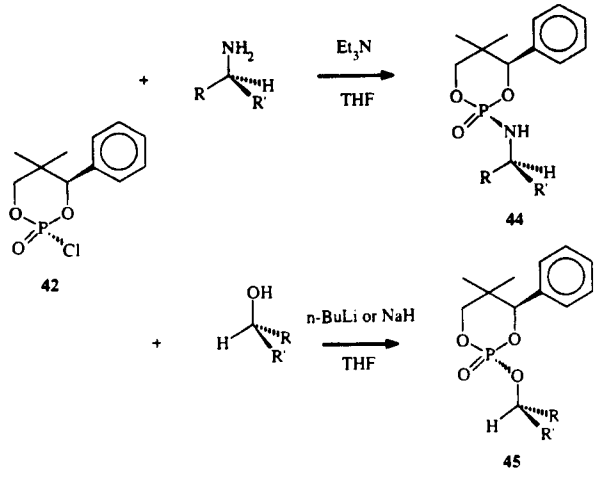
Scheme 13.

means of reaction with PCl_5. This synthetic protocol allows large structural variation in the substituents on the phenyl moiety and, moreover, guarantees the availability of both enantiomers of the derivatizing reagent.

Chiral primary amines and esters of amino acids react with **42** using Et_3N as base in THF at reflux temperature to afford diastereomeric amides **44**. Chiral secondary amines and alcohols require more forcing conditions, although with n-butyllithium in THF at room temperature the corresponding amides **44** and esters **45** are obtained in quantitative yields (Scheme 14). The same holds for the thio analogue **43**.

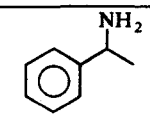
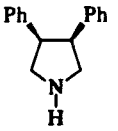
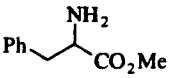
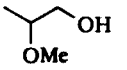
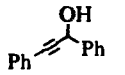
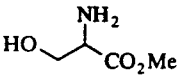
Diastereomeric amides **44** and esters **45** can be analyzed by means of ^1H and ^{31}P NMR, although the latter is preferred. As long as the substrates are stable towards the basic conditions needed to achieve adequate coupling, large structural variations in substrate are tolerated. The use of *n*-butyllithium or NaH makes this method of limited use with respect to multifunctional substrates. Some representative examples are given in Table III.

As can be seen from Scheme 14, amide formation proceeds with inversion of configuration at the phosphorus center, whereas the esters are formed with complete retention of configuration as proven by extensive 2D NMR (NOESY) and X-ray studies[52,53]. The reactions normally proceed without the formation of side products, although sometimes small amounts of pyrophosphate **46** are formed (Scheme 13), which is recognized by a ^{31}P NMR signal at δ −20.56 ppm. The formation of **46**, however, does not influence the actual *ee* determination[54].



Scheme 14.

Table III ^{31}P*-NMR diastereomeric shift differences of products* ***44*** *and* ***45*** *obtained from* ***42*** *and racemic alcohols and amines, recorded in* $CDCl_3$*; 0.01 M.*

D,L-Compound	Δδ (ppm)
	0.63
	0.48
	0.51
	0.07
	0.17
	0.20

Insight in the structural requirements needed for efficient derivatizing reagents that show large shift dispersion for the diastereomeric adducts could lead to a more rational design of this type of reagents. On comparison of the derivatizing reagents described so far a number of important conclusions can be drawn:

(*i*) The largest diastereomeric chemical shift dispersion is found when diastereomeric phosphorothioic amides or esters instead of the corresponding oxygen analogues are used, although the diazaphospholidines[46] show an inverse behaviour.

(*ii*) On comparison of chiral amines, thiols and alcohols the following order of diastereomeric shift dispersion is found for the adducts: amine > thiol > alcohol.

(*iii*) The chemical shift behaviour of the diastereomeric products is very sensitive to temperature and solvent polarity effects.

(*iv*) The lower reactivity of the chlorophospholane sulfides **43** limites their use to substrates that are not sensitive to treatment with strong base.

Because of the large structural differences of the derivatizing agents described so far, it would be desirable if a reagent was available that is easily modified systematically without changing its most important stereochemical features.

Fortunately, we were able to develop new chiral chlorophosphorinane oxides and sulfides **47–50**, based upon enantiomerically pure amino alcohols[55], which are structurally related to chlorophosphorinane **42** and the thio analogue **43** (Scheme 15).

The new chlorophosphorinanes provide upon reaction with D,L-alanine methyl ester the corresponding diastereomeric phosphorus amides **51**, **53** and **55**, using Et_3N as base and CH_2Cl_2 as solvent at reflux temperature. Due to the lower reactivity of thio analogues **43**, **48** and **50**, the addition of a catalytic amount of 4-(dimethylamino)pyridine was required to obtain the amides **52**, **54** and **56**, respectively (Scheme 15).

For **51**, the observed shift difference ($\Delta\delta$ 0.066 ppm) is comparable with the diastereomeric shift dispersion of thio-analogue **52** ($\Delta\delta$ 0.053 ppm) (Table IV). However, when the diastereomeric adducts **53** and **54** are compared the latter gives a large shift dispersion of $\Delta\delta$ 2.01 ppm

Table IV ^{31}P-NMR data of diastereomeric adducts of D,L-AlaOMe 51–56, recorded in $CDCl_3$; 0.01 M.

Adduct	δ (ppm)	Δδ (ppm)	Ratio
51	3.15	0.066	49.5:50.5
52	−18.34	0.053	49:51
53	24.12	0.487	49:51
54	62.15	2.011	48.5:51.5
55	18.91	0.365	49:51
56	58.12	1.897	48:52

(illustrated in Figure 1) compared to Δδ 0.487 ppm for the former. The same tendency is observed for the adducts **55** and **56**.

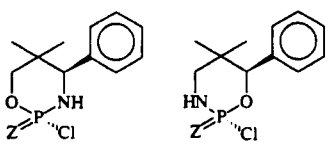
Reactions with the thio derivatives, however, proved to be more troublesome than with the oxygen analogues. The use of stronger basic conditions results in unfavourable side reactions like *i.e.* ring opening and polymerization.

In conclusion, pentavalent phosphorus reagents have shown to be efficient and successful derivatizing reagents for alcohols, amines and thiols, showing moderate to excellent diastereomeric shift dispersion. Moreover, by using the readily available phosphorus chlorides **42**, **43** and **47–50**, tuning of the reactivity and the obtained diastereomeric shifts is possible by relatively simple structural modifications.

II.B Chiral pentavalent phosphonates as derivatizing reagents for aqueous solutions

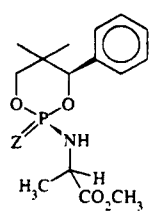
Due to the low solubility of amino acids in organic solvents, methods for the *ee* determination of unprotected amino acids are scarce. It would therefore be of interest to have access to methods based on chiral phosphorus derivatizing reagents capable of derivatizing amino acids in water or aqueous solutions. As mentioned before (*vide supra*), pentavalent chlorophospholane oxides and sulfides are not suitable for use in aqueous solutions. Fortunately, by employing the *Atherton-Openshaw-Todd* reaction phosphonic amides can be obtained from dibenzyl phosphonate and amines using CCl_4 and *strong* bases as reagents[56]. Moreover, *Zhao* and co-workers[57] reported that on using *weakly* basic conditions, α-amino acids are easily transformed into *N*-(diisopropylphosphoryl)-amino acids in aqueous media using diisopropyl phosphonate, CCl_4 and Et_3N as reagents.

This led us to develop C_2-symmetrical phosphonate **57**, which is readily accessible from commercially available

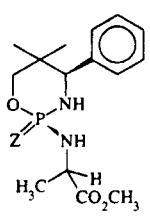


47 Z= O
48 Z= S

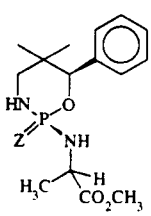
49 Z= O
50 Z= S



51 Z = O
52 Z = S



53 Z = O
54 Z = S



55 Z = O
56 Z = S

Scheme 15.

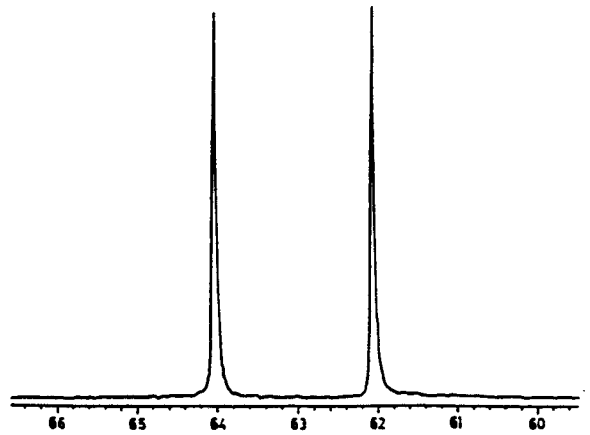


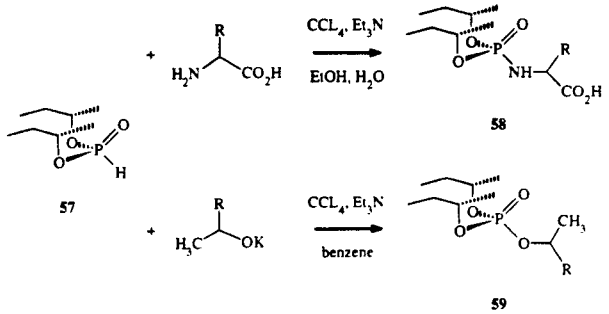
Figure 1. ^{31}P-NMR spectrum of adduct **54** *using racemic alanine methyl ester.*

(*S*)-butan-2-ol and PCl_3[58]. Chiral amino acids are quantitatively transferred into the diastereomeric amides **58** upon treatment with phosphonate **57**, CCl_4 and Et_3N in ethanol water mixtures[59,60] (Scheme 16).

After extraction of the crude reaction mixture with ethyl acetate, the obtained diastereomeric phosphonate amides **58** and esters **59** are analyzed by means of ^{31}P NMR. Alternatively, ^{1}H NMR can be used, although the spectra do not always allow proper quantification due to excessive H–H and P–H coupling. The method allows large structural variations since also amines, alcohols, amino acid esters, amino acid amides and sterically hindered α-alkylated amino acids can be analyzed. When amines and alcohols are to be analyzed, water can be omitted as (co)-solvent. Moreover, when alcohols are analyzed, more forcing coupling conditions (KO^{t}Bu) are required. Typically, the diastereomeric shift dispersions for **58** and **59** in the decoupled ^{31}P NMR spectra ranges from Δδ 0.079 ppm (D,L-serine) to Δδ 0.487 ppm (D,L-α-methylphenylglycine) for amines and amino acids and from Δδ 0.103 ppm (D,L-α-methylbenzenemethanol) to Δδ 0.127 ppm (D,L-menthol) for alcohols. Typical ^{31}P NMR data are collected in Table V.

The diastereomeric shift dispersions compare favourably with those obtained by using other chiral derivatizing agents, which illustrates the advantage of ^{31}P NMR analysis; only two signals are obtained in the case racemic amino acids are used whereas other methods are based upon using the (multiplet) ^{1}H NMR signals (Figure 2).

The method not only allows broad structural variation in substrate but also in solvents; besides ethanol water solvent systems, CH_2Cl_2, $CHCl_3$, THF, benzene and combinations of these can be used. The most important feature of this new method is the *easy derivatization of unprotected amino acids in aqueous solutions* and the subsequent



Scheme 16.

ee determination by means of ^{31}P NMR. Moreover, reagent **57** is easily formed from commercially available starting materials and is very stable.

Although phosphonate **57** is readily coupled with amino acids, an increase in diastereomeric shift differences is sometimes warranted. Therefore, phosphorinane **60** which strongly resembles chlorophosphophosphorinane **42** was developed as an alternative derivatizing reagent for aqueous media[61] (Scheme 17).

Phosphorinane **60** reacts with a variety of nucleophiles including chiral alcohols, amines, amino acid esters and unprotected amino acids using CCl_4 and Et_3N as reagents and ethanol containing solvent mixtures. Furthermore, water is acceptable as (co)-solvent if desired when unprotected amino acids are allowed to react with reagent **60**. After extraction of the crude reaction mixture with ethyl acetate or chloroform, the diastereomeric phosphonate amides **44**, amide acids **61** and esters **45** are analyzed by means of ^{31}P NMR.

It appears that large substituents, such as a phenyl group present in the substrate, usually have a positive influence upon the diastereomeric shift dispersion of products **44**, **45** and **61**. Using amino acids, the diastereomeric shift differences are the largest for D,L-phenylglycine ($\Delta\delta$ 1.218 ppm) and relatively small for D,L-alanine ($\Delta\delta$ 0.256 ppm)[62]. Also α-alkylated amino acids and amino acid amides can be analyzed, which give diastereomeric shift differences between $\Delta\delta$ 0.786 ppm for D,L-α-methylphenylalanine amide and $\Delta\delta$ 1.653 ppm (D,L-α-methylphenylglycine). These products, however, are less easily formed compared to the α-amino acids probably due to steric hindrance by the α-alkyl group. The ester protected amino acids show only little differentiation in the diastereomeric chemical shift dispersion, except for D,L-α-methylserine, which appears to be coupled through the alcohol group rather than the amine functionality (δ −7.45 ppm, $\Delta\delta$ 0.201 ppm).

It is important to note that, although the reaction conditions and the derivatizing reagents **42** and **60** are different, the products as well as the stereochemistry at the phosphorus center are the same upon the use of chiral alcohols, amines and amino acid esters as substrates.

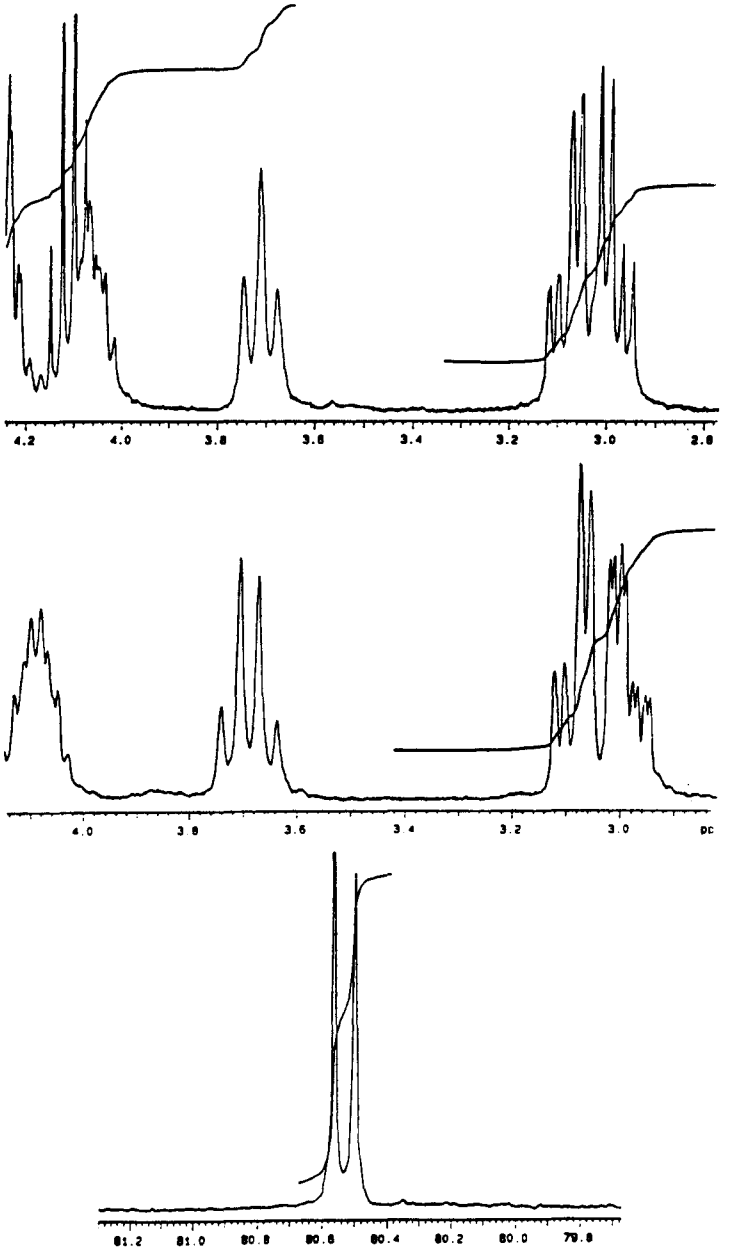
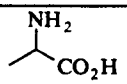
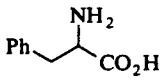
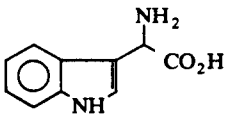
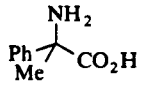
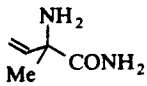
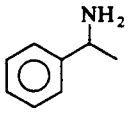
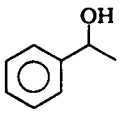


Figure 2. (a) Selected part of the ^1H spectrum of 58 using D-Phe and (b) D,L-Phe. (c) ^{31}P-NMR spectrum of adduct 58 using D,L-Phe recorded in $CDCl_3$; 0.1 M.

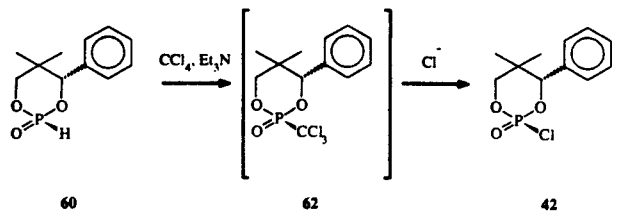
Table V ^{31}P-NMR diastereomeric chemical shift differences of products 58 and 59, recorded in $CDCl_3$; 0.01 M.

D,L-Compound	$\Delta\delta$ (ppm)
	0.116
	0.106
	0.091
	0.487
	0.185
	0.185
	0.103

Based upon the X-ray structures of **42** and the corresponding amides **44** and esters **45**, extensive 2D NMR NOE experiments and the fact that reagent **42** does not tolerate water as (co)-solvent, it is concluded that the reactive intermediates are probably not the same[63], and we suggest that the derivatization reaction proceeds via trichloromethyl ester **62** (Scheme 18).

Since it is known that large substituents at phosphorus preferentially assume the axial position, leaving the double bonded oxygen in the equatorial position, the most likely route involves two subsequent retentions of configuration on the phosphorus center when alcohols are allowed to react and one retention followed by an inversion of configuration on reaction of amines or amine containing substrates.

In conclusion, reagents **57** and **60** show excellent shift differences for the diastereomeric amide **44**, **58** and **61**



60 **62** **42**

Scheme 18.

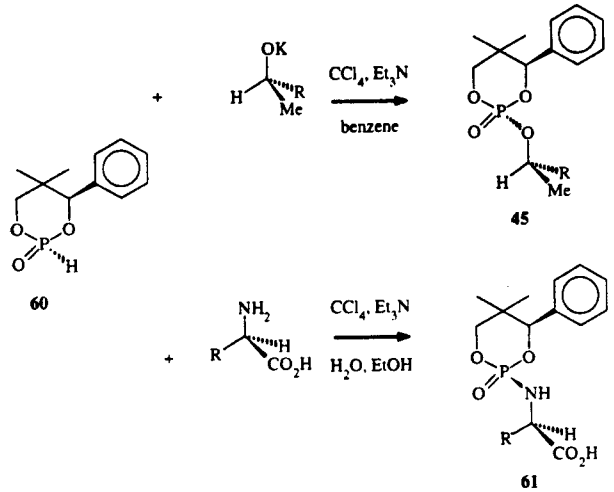
and ester **45** and **59** derivatives using ^{31}P NMR. Both of the enantiomers of derivatizing reagents **57** and **60** are available and structural variations are easily introduced. Moreover, large variations in the derivatizing conditions, for example the use of aqueous media, and substrate structure including unprotected amino acids and α-alkylated amino acids, are tolerated.

It is well established that diastereomeric shift differences respond to steric effects, non-bonded interactions and conformational mobility in the diastereomeric derivatives[64], affording larger shift differences for diastereomers that are conformationally more restricted. Adducts **64** were designed to meet such requirements. The protonated amine moiety in **64** could possibly conformationally lock the deprotonated acid part of the molecule by means of intramolecular ion pair formation (Scheme 19), and the conformational locked-unlocked equilibrium should be strongly pH dependent.

Diastereomeric amides **64** are obtained upon treatment of derivatizing reagent **63** with CCl_4, Et_3N and racemic amino acids (*vide supra*), and can be analyzed by means of ^{1}H and ^{31}P NMR[65].

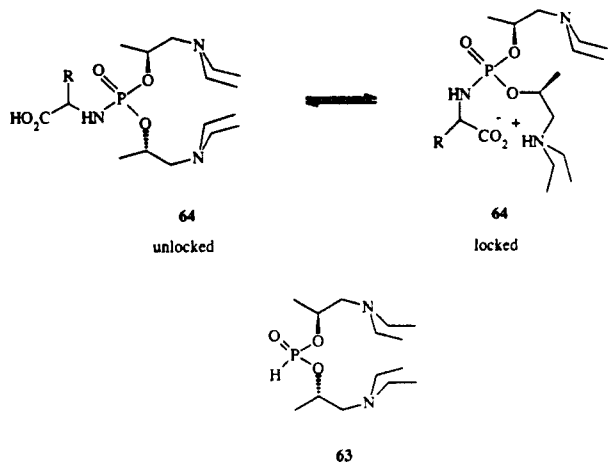
The observed diastereomeric shift dispersion (^{31}P NMR) shows, as expected, a large pH dependency. Using *e.g.* D,L-alanine as substrate, shift differences are significantly higher in the pH range from 4.5 to 8.0, reaching a maximum value at pH 7 (Figure 3).

However, within this pH domain 4.5 to 8.0, the deviations are relatively small. At low pH, the protonation of the carboxylic group probably gives rise to a situation in which the intramolecular tight ion pair no longer exists. At high pH, total deprotonation takes place and also results in a situation where tight ion pair contributions vanish. With D,L-phenylglycine as substrate, analogous behaviour is found. This phenomenon is not observed when amines are used as substrates, strongly suggesting that some kind of conformational locking must be in operation in the pH 4.5 to 8.0 domain with amino acids. Unfortunately, decomposition above pH 10 was observed.



60 **45** **61**

Scheme 17.



64 unlocked **64** locked **63**

Scheme 19.

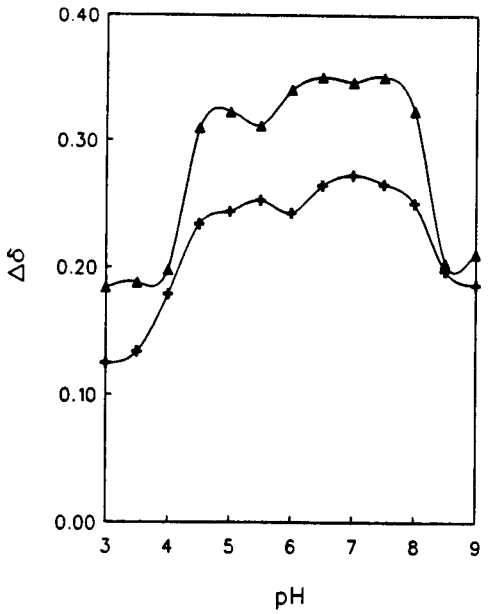


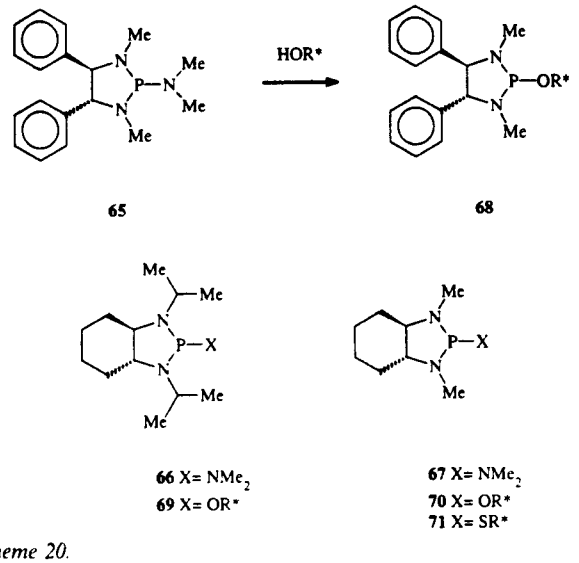
Figure 3. Diastereomeric shift differences vs. pH of **64** *with* D,L-*Ala (+) and* D,L-*PG (▲) recorded in D_2O; 0.01 M.*

Although reagent **63** can be used for the *ee* determination of unprotected amino acids in aqueous solutions, the low stability of **63** and the adducts **64** limit the scope. It was, however, shown that tuning of the derivatizing reagents and the products by changing the pH of the solution is possible. This remarkable behaviour can be rationalized by a conformational locking model and can be used as a model for further developments towards a more rational design of chiral derivatizing reagents.

II.C Trivalent phosphorus derivatizing reagents

As shown by *Burgada* and *Mukaiyama* in 1966[66], exocyclic P–N bonds of amino-phosphines are very easily cleaved by alcohols[67], thiols and amines. *Alexakis* and co-workers[68] recently used this principle for the development of chiral derivatizing reagents based on trivalent phospholidines (Scheme 20).

Derivatizing reagents **65**, **66** and **67** are obtained by amine exchange of the appropriate C_2-symmetrical diamines with HMPT. These trivalent phosphorus reagents are stable



Scheme 20.

Table VI ^{31}P-NMR diastereomeric shift differences of **70** *obtained from reagent* **67** *and racemic alcohols, recorded in C_6D_6; 0.1 M.*

D,L-Alcohol	Δδ (ppm)
2-Methylbutan-1-ol	0.202
β-citronellol	0.538
butan-2-ol	3.702
menthol	6.259
Ephedrine	11.442
α-ethyl-α-methylbenzenemethanol	1.728

for months under an inert atmosphere although they are very sensitive to moisture.

Reagents **65**, **66** and **67** are very reactive and diastereomeric derivatives **68**, **69** and **70** are readily formed upon reaction with a large variety of chiral primary, secondary and *tertiary* alcohols without the necessity of additional reagents by simple stirring in C_6D_6 at 20°C.

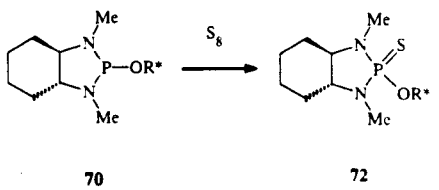
Diastereomeric adducts **68–70** can be analyzed directly without the need of isolation and/or purification by means of ^1H or ^{31}P NMR, although the latter is preferred. The largest diastereomeric shift dispersions are obtained for derivatives **70** prepared from reagent **67** (See Table VI for some selected examples).

For example with D,L-butan-2-ol, the diastereomeric shift dispersion (Δδ 3.702 ppm) compares favourably with the values previously obtained by *Shapiro*[38] (Δδ 0.0056 ppm), by *Johnson*[41] (Δδ 0.200 ppm) and the closely related pentavalent adduct **38**[46] (Δδ 0.269 ppm). In contrast to allylic alcohols, which are readily analyzed, prop-2-yn-1-ols undergo rapid [2,3]-sigmatropic rearrangement[69]. The initially formed chiral phosphoallene reacts with the dimethylamine produced upon cleavage of the P–N bond to afford ultimately an enamine with loss of the stereocenter in the former alcohol[70].

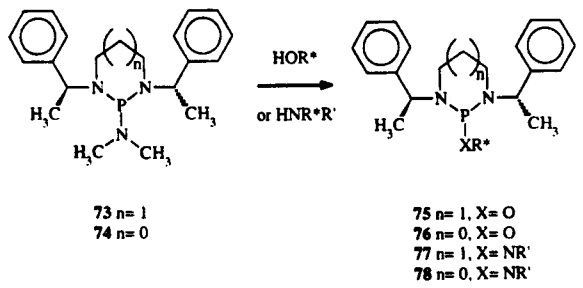
The use of diols as substrate gives rise to the formation of dioxaphospholanes with cleavage of the diazaphospholane ring. The phosphorus atom becomes a new stereogenic center, resulting in many signals in the ^{31}P NMR spectrum that cannot be quantified properly. Also chiral thiols can be analyzed with reagent **67**. Diastereomeric thiazaphospholanes **71** are formed, for which excellent diastereomeric shift dispersions are obtained. With D,L-2-butanethiol as substrate, Δδ is 1.82 ppm.

For most of the examples shown, ^1H and ^{13}C NMR also allow *ee* determination, although ^{31}P NMR is preferred for its superior diastereomeric shift dispersion and simple spectra. It should be noted that the ^1H spectra of these derivatives are often very complex, due to extensive P–H and H–H coupling.

Diastereomeric derivatives **69–71** are not stable to TLC or GC analysis. However, virtually instantaneous reaction with sulfur (S_8) powder provides air stable derivatives **72** quantitatively as shown for **70** (Scheme 21). Many of these derivatives can be analyzed by means of GC or alternatively by means of HPLC to afford baseline separation that allow easy and accurate quantification. Moreover, these pentavalent thio derivatives can be analyzed by means of ^{31}P NMR, although the shift differences are much smaller compared to the trivalent derivatives[71].



Scheme 21.



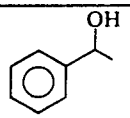
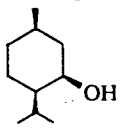
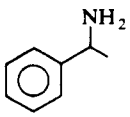
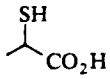
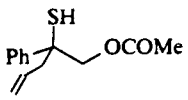
Scheme 22.

We introduced phospholidines based upon the very cheap (*R*) or (*S*) α-methylbenzenemethanamine[72]. Reagents **73** and **74**[73] react with a variety of chiral alcohols, but also with amines, esters of amino acids, thiols, α-sulfanyl acids and the corresponding mercapto esters affording diastereomeric adducts **75–78** (Scheme 22).

We were also able to functionalize several free amino acids by using reagent **73** under phase transfer conditions (solid-liquid phase).

The diastereomeric shift differences of derivatives **75–78** are comparable with the results as obtained by *Alexakis* and co-workers (Table VII). An example is shown in Figure 4. Furthermore, the same side reactions, as described by *Alexakis* and co-workers (*vide supra*), were observed including a [2,3]-sigmatropic rearrangement with propynols and an intramolecular cyclization reaction when using diols.

Table VII ^{31}*P-NMR diastereomeric shift differences of products 75 and 77, recorded in* $CDCl_3$*; 0.1 M.*

D,L-Compound		Δδ (ppm)
	α-methylbenzenemethanol	1.38
	butan-2-ol	2.73
	menthol	1.69
	[1*R*-(1α,2β,5α)]-5-methyl-2-(1-methylethyl)cyclohexanol	
	α-methylbenzenemethanamine	2.46
	[2*S*-(2α,5β)]-2,5-dimethylpyrrolidine	1.31
	2-sulfanylpropanoic acid	2.30
	β-(prop-2-enyl)-β-sulfanylbenzeneethanol, acetate	0.53

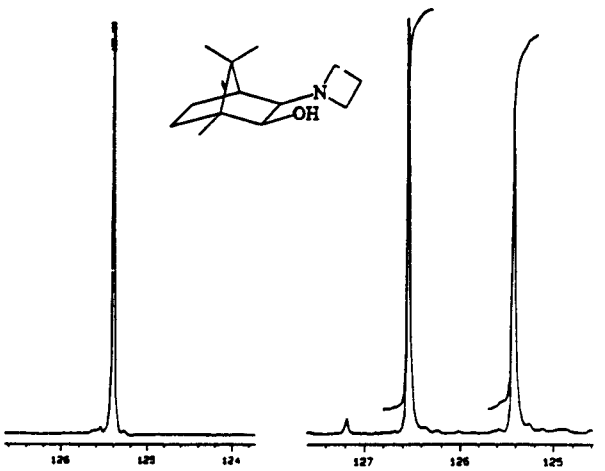
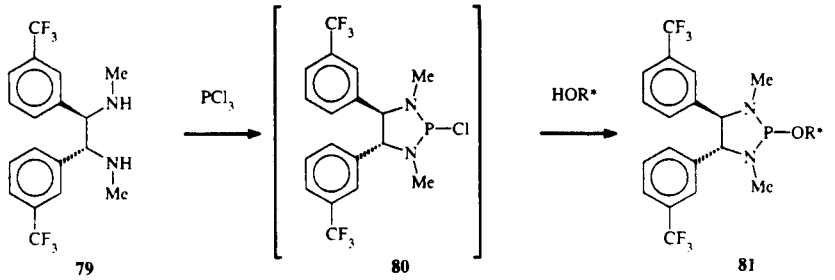


Figure 4. ^{31}*P-NMR spectra of 76 coupled with enantiomerically pure (a) and racemic (b) cis-exo-3-(1-azetidinyl)isoborneol [Feringa et al., Tetrahedron 50, 4479 (1994)].*

To overcome these problems encountered with propynols and diols, which are probably due to the reactivity of reagents **65–67**, recently a new derivatizing protocol was developed by *Alexakis* and co-workers in which the reactive exocyclic P–NMe_2 moiety was replaced by a better but less basic leaving group[74]. Thus, an appropriate C_2-symmetrical chiral diamine, for example **79**, is allowed to react with one equivalent of PCl_3 in the presence of excess base (Et_3N, pyridine etc.) leading to the *in situ* formation of the derivatizing reagent **80**. This reagent is subsequently allowed to react with chiral alcohols, thiols or, due to its higher reactivity also with chiral *amines* (Scheme 23).

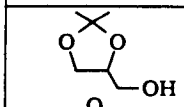
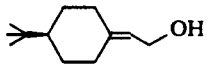
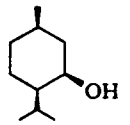
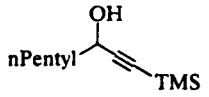
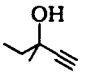
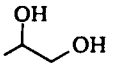
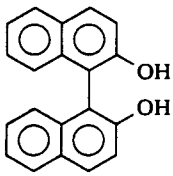
The entire derivatization reaction is performed in an NMR tube using $CDCl_3$ or CH_2Cl_2. It should be noted that the products using this new procedure are the same as those obtained from using reagents **65–67**. In addition, owing to the higher reactivity also propynols and/or hindered alcohols will enter into reaction (See Table VIII for some selected examples).

As expected, it is possible to analyze propynols without any problem using this new protocol. Also 1,2 and 1,3 diols can be analyzed since the intermolecular reaction is faster than the intramolecular cyclization reaction due to the higher reactivity of the *in situ* prepared **80**. Furthermore, it is possible to transfer the adducts quantitatively



Scheme 23.

*Table VIII ^{31}P-NMR diastereomeric shift differences of **81** obtained from racemic alcohols and **79** with PCl_3, recorded in $CDCl_3$; 0.2 M.*

D,L-alcohol		Δδ (ppm)
	2,2-dimethyl-1,3-dioxolane-4-methanol	0.748
	3-ethynyloxirane-2-methanol	0.905
	2-[4-(*tert*-butyl)cyclohexylidene]ethanol	0
	menthol	2.759
	1-(trimethylsilyl)oct-1-yn-3-ol	4.913
	3-methylpent-1-yn-3-ol	0.479
	propane-1,2-diol	0.202
	[1,1'-binaphthalene]-2,2'-diol	0.202

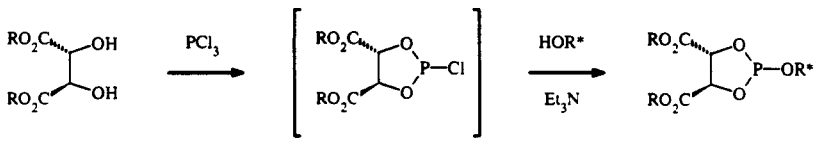
into the air stable pentavalent phosphonothioates or -selenoates by reaction with sulfur (S_8) (*vide supra*) or selenium (Se_8) powder. Compared to the sulfur adducts, selenium adducts show a larger diastereomeric shift dispersion and very sharp signals in the ^{31}P NMR spectra. Moreover, selenium compounds can be analyzed by means of ^{77}Se NMR[75].

By using this new protocol very good reactivity is obtained allowing the analyses of a large variety of sensitive alcohols, thiols and amines. The adducts show excellent diastereomeric shift dispersion in the ^{31}P-NMR spectra and the derivatizing reagents can easily be modified.

It was shown by *Buono* and co-workers[76], however, that trivalent dioxaphospholanes can be used as derivatizing reagents for the *ee* determination of chiral alcohols. Using diesters of (*R,R*)-tartaric acid **82** as C_2-symmetrical building block, they were able to functionalize these reagents *in situ* by reaction with PCl_3 into the trivalent phosphorus reagent **83**, which reacts readily with chiral alcohols upon the addition of Et_3N as base (Scheme 24).

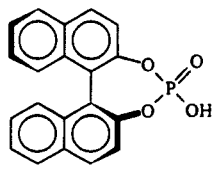
A variety of alcohols was derivatized quantitatively, and the diastereomeric products **84** were shown to give small to moderate Δδ values, *i.e.* for D,L-α-methylbenzenemethanol and D,L-menthol Δδ values of 1.4 and 0.4 ppm were found, respectively.

The method allows easy structural modification in the ester part and is based upon the use of the cheap C_2-symmetrical tartaric acid. A major drawback, connected with the use of all the trivalent phosphorus derivatizing reagents treated here, is the high sensitivity to moisture and problems related herewith.

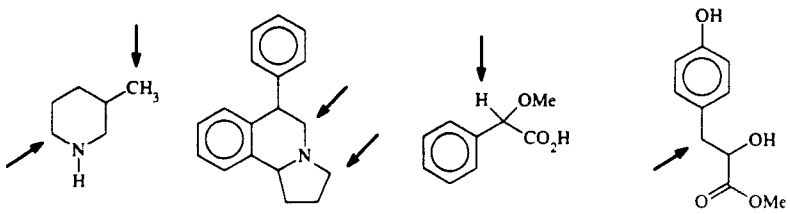


82 **83** **84**

Scheme 24.

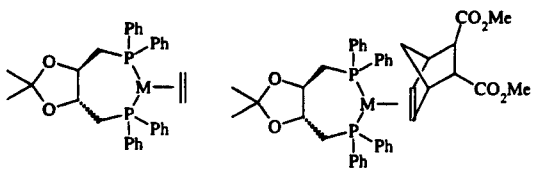


85



86 **87** **88** **89**

Scheme 25. Arrows indicate signals that show diastereotopicity (see text).



90 M = Pt
91 M = Pd

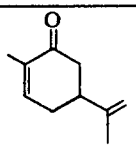
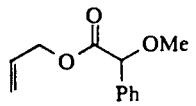
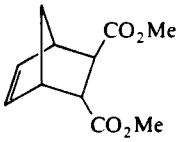
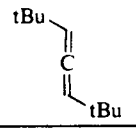
92

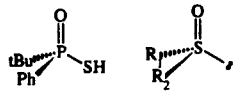
Scheme 26.

II.D Phosphorus reagents based on non-covalent diastereomeric interactions

It is also possible to form diastereomers by means of noncovalent interactions, and several phosphorus methods have been developed based on this principle.
The utility of (*R*) or (*S*)-1,1'-binaphthalene-2,2'-diyl hydrogen phosphate (**85**, *BNHP*) as chiral complexing agent for chiral amines[77] was shown by *Shapiro* and *Jarema*[78] (Scheme 25).
The derivatization procedure consists of salt formation by simply mixing one equivalent of amine and of *BNHP* in $CDCl_3$ or C_6D_6. The *ee* is subsequently determined by means of ^{1}H-NMR using the diastereotopic shifts of substrate protons[79]. Often more than one signal allows quantification. For the cyclic amines **86** and **87**, respectively, two ($\Delta\Delta\delta$ 0.161 and 0.246 ppm) and three ($\Delta\Delta\delta$ 0.147, 0.016 and 0.067 ppm) different proton signals can be used for analysis (Scheme 25). By using the *BNHP*-pyridine-d_5 salt[80] it was possible to determine the *ee* of two non-amine materials (**88** and **89**, Scheme 25), although the diastereomeric shift dispersion ($\Delta\Delta\delta$ 0.005 and 0.006 ppm) is only of importance when high fields are applied. The method, however, is very easy to perform and appears to be very accurate; enantiomeric impurities as low as 0.5% were detected without any problems.
Parker and *Taylor*[81] used organometallic C_2-symmetric biphosphine ethene complexes **90** and **91** based on zerovalent platinum and palladium for the *in-situ* ^{31}P NMR assay of the enantiomeric purity of several chiral η^2 donors (Scheme 26).

*Table IX ^{31}P-NMR diastereomeric non-equivalences of **90** using **91** and racemic alkenes, recorded in C_6D_6; 0.02 M. $\Delta\delta_a$ arbitrarily assigned as resonating at higher frequency.*

D,L-Alkene	$\Delta\delta_a$ (ppm)	$\Delta\delta_b$ (ppm)
	1.1	1.02
	0.9	0.2
	0.3	0.7
	0.9 (Si bound)	0.23 (Si bound) 1.20 (Re bound)



93 **94**

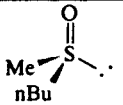
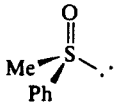
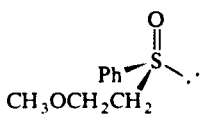
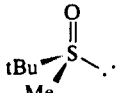
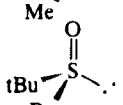
Scheme 27.

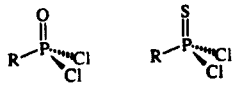
The displacement of ethene with alkynes, allenes and electron-poor or strained alkenes proceeds readily in THF or C_6D_6, yielding diastereomeric complexes **92** that show good chemical shift dispersion (Table IX). The spectral analysis may be complicated since binding to the *Si* or *Re* face of a non-C_2-symmetric two electron donor gives rise to constitutionally isomeric species. Furthermore, the decoupled ^{31}P-NMR spectra show also two different platinum couplings for each diastereomer.
Although the troublesome spectral interpretation can be seen as a drawback, the method readily affords the *ee* of a class of substrates that is difficult to analyze by other NMR methods[82].
Mikozłajczyk and co-workers[83] reported the use of (*S*)-(*tert*-butyl)phenylphosphinothioc acid (**93**) as a chiral solvating agent for the *ee* determination of chiral sulfoxides **94** (Scheme 27).
The procedure for the enantiomeric analysis consists of the mixing of one equivalent of the chiral sulfoxide and one or two equivalents of the phosphoryl compound in C_6D_6. The diastereomeric solvatation complexes are analyzed by means of ^{1}H-NMR; small diastereomeric shift dispersions are obtained for signals in the (partly) racemic substrates. Some typical values are collected in Table X. The observed spectral non-equivalences for the diastereomeric complexes are probably due to the formation of hydrogen bonded complexes or ion pairs[84].

III Achiral phosphorus reagents

Although *Ladenburg* as early as 1895[85] showed that mixing of (*R*)- and (*S*)-coniine was accompanied by a change in temperature and *Uskoković* and co-workers[86] were able to demonstrate the nonequivalence of the NMR

*Table X ^{1}H-NMR non-equivalences of diastereomeric phosphinothioic sulfoxide complexes obtained from **93** and racemic **94**, recorded in C_6D_6.*

D,L-Sulfoxide	$\Delta\delta$ (ppm)
	0.050
	0.003
	0.030
	0.014
	0.043



95 R= alkyl **96** R= alkyl

Scheme 28.

spectra of racemic and optically active dihydroquinine, it is only in recent years that the existence of diastereomeric interactions between enantiomers in solution has been fully appreciated[87,88,89].

The consequences of the differences in chemical reactivity and product composition between a single enantiomer (*R* or *S* isomer) or the (partly) racemic compound (*R* and *S* isomers), due to enantiomer recognition and interactions, have been discussed by *Wynberg* and *Feringa*[87]. Chiral self-recognition leading to non-linear effects in asymmetric synthesis has now several precedents[87-90].

Horeau was the first to recognize the potential of using the intrinsic differences in chirality of an enantiomerically pure and (partly) racemic substrate for *ee* determination. When two enantiomers dimerize (Eqn. 1), either via covalent bond formation or via noncovalent associative interactions, diastereomers are formed in the (partly) racemic case.

$$R \longrightarrow RR$$

$$R + S \longrightarrow RR + SS + RS\ (SR) \qquad (1)$$

If the enantiomers are coupled via an achiral agent A, a single isomer *R–A–R* is obtained with an enantiomerically pure substrate whereas two diastereomers *R–A–R* (*S–A–S*), a D,L-pair, and *R–A–S* (*S–A–R*), a *meso* compound, are formed starting from a racemic substrate (Eqn. 2).

$$R + A \longrightarrow R\text{–}A\text{–}R$$

$$R + S + A \longrightarrow \underset{\text{D,L pair}}{\underset{S\text{–}A\text{–}S}{R\text{–}A\text{–}R}} + \underset{\text{meso}}{R\text{–}A\text{–}S\ (S\text{–}A\text{–}R)} \qquad (2)$$

We found that the differences in properties between the diastereomers can be used for *ee* determination provided that the coupling reagent A fulfills in number of requirements:

(*i*) The coupling reaction proceeds in high yield, preferably with quantitative conversions.

(*ii*) No deviation from the statistical ratios of coupled products occurs (no antipodal effects).

(*iii*) Chemical shift differences of the diastereomeric products are large enough to ensure accurate integration.

(*iv*) It is highly desirable that agent A contains a unique atom that makes analysis of each diastereomer via a single NMR absorption possible, *e.g.* that A contains a spectator atom.

The phosphorus nucleus is highly suitable for this purpose in view of the great advantage of ^{1}H-decoupled ^{31}P-NMR

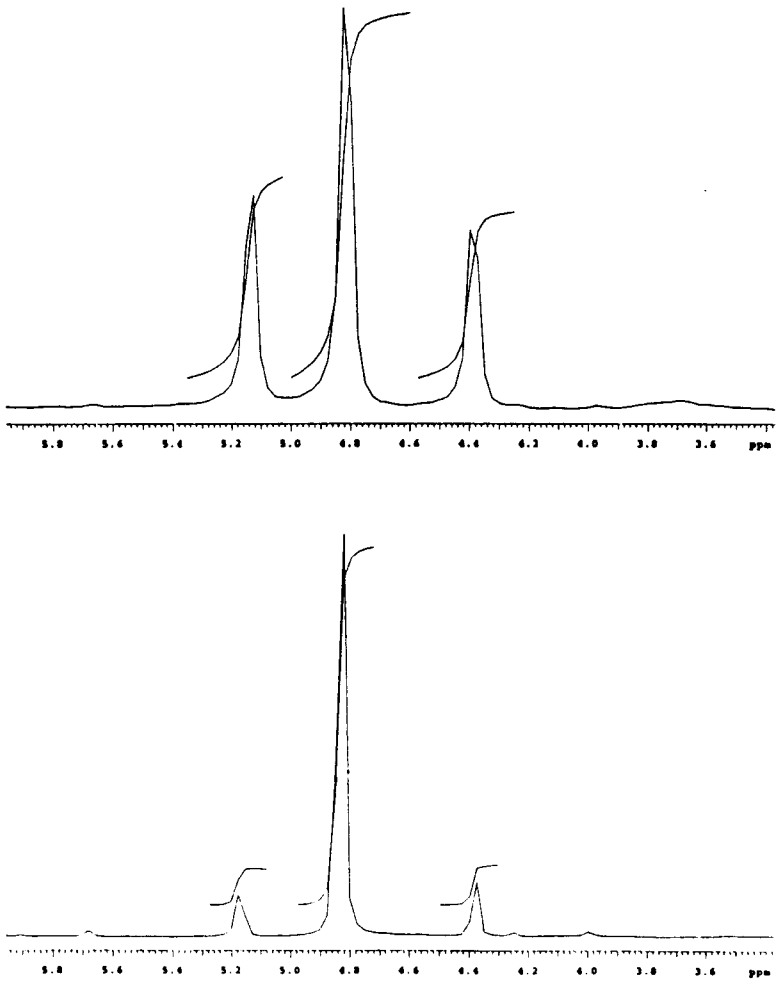
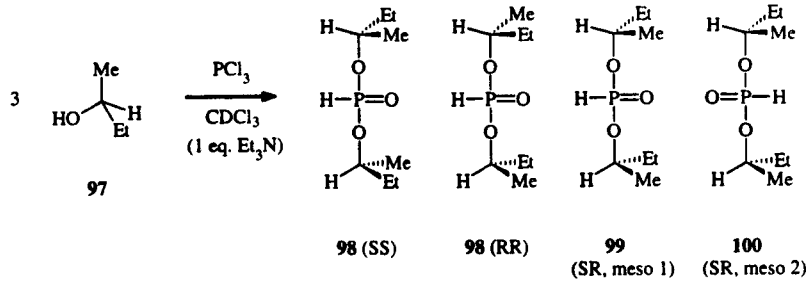


Figure 5. ^{31}P-NMR spectra of reaction of racemic **97** *(a) and enriched* **97** *(81% ee, b) with PCl_3 recorded in $CDCl_3$; 0.01 M.*



Scheme 29.

for *ee* determination using chiral derivatizing agents (*vide supra*).
Several *ee* determination methods based on PCl_3, $RP(=O)Cl_2$ (**95**) or $RP(=S)Cl_2$ (**96**) as achiral phosphorus derivatizing agents have been developed by us (Scheme 28).

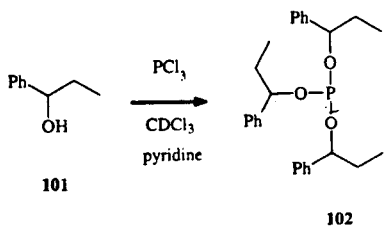
III.A PCl_3 method[91]

Using PCl_3 in deuteriochloroform various chiral alcohols are converted in diastereomeric phosphonates in the absence or presence of an equivalent of base in a fast and quantitative reaction via initial phosphite formation followed by an Arbuzov rearrangement. Application of this reaction for the *ee* determination is illustrated for butan-2-ol **97**. Racemic **97** yields a mixture of phosphonates **98** (*R,R*, *S,S*), **99** (*R,S*, meso-1) and **100** (*R,S*, meso-2) in a 2:1:1 ratio (Scheme **29**).
The formation of two *meso*-phosphonates **99** and **100** is due to the presence of a stereogenic, achirotopic phosphorus center. The ^1H decoupled ^{31}P NMR spectrum of the reaction mixture of racemic **97** shows three well separated singlet signals in the expected ratio for the diastereomers **98**, **99** and **100** (Figure 5[a]). Enantiomerically pure (*S*)-**97** yields exclusively (*S,S*)-**98** resulting in the absence of the meso-absorptions (Figure 5[b]).
For (partially) enriched alcohols the absorptions of the *meso* isomers decrease relative to the absorptions of the D,L-pair. The enantiomeric excess ($p \times 100$; p = enantiomeric purity) is calculated from the integrated signal areas Q and Q' of the D,L and *meso* isomers, respectively, with D,L/*meso* ratio $K = Q/Q'$ using *Horeau*'s formula $p^2 = (K-1)/(K+1)$.
It was shown by independent *ee* determinations that no racemization during phosphonate formation occurs and that loss of part of the alcohol as the halide does not affect the accuracy. Typical examples of chiral alcohols analyzed via this technique are given in Table XI.
The method tolerates large variations in the alcohol structure, *e.g.* primary, secondary, benzylic and allylic alcohols and α-hydroxy-esters and amides. Baseline separations were found except for borneol. Chiral recognition during phosphonate formation is neglible. Even for the case of hindered alcohols, such as menthol, only small deviations (< 3%) from the expected ratios are observed.

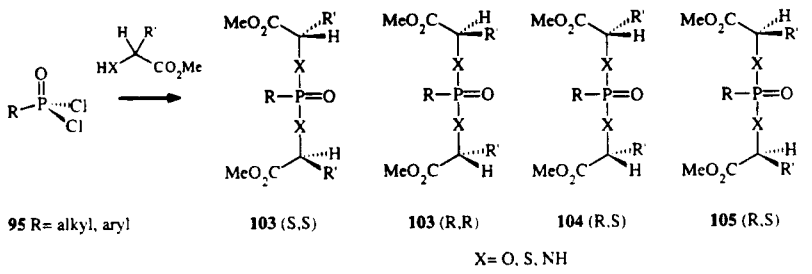
Table XI Some of the alcohols analyzed using the PCl_3 method (Δδ [meso,meso, D,L] in Hz in parenthesis).

D,L-Alcohols	Δδ (*meso, meso*, D,L)
butan-2-ol	454, 387, 425
3-hydroxytetrahydrofuran	481, 447, 464
menthol	459, 309, 413
α-methylbenzenemethanol	416, 344, 370
4-[2-furyl]-butan-2-ol	449, 395, 433
β-ethylbenzeneethanol	652, 590, 623
buten-3-en-2-ol	393, 349, 369
cyclohex-2-en-1-ol	450, 416, 432

Important advantages of the PCl_3 method are the cheap achiral reagent employed, the very fast and easy (*in situ*) *ee* determination without the necessity of product isolation and purification. Major drawbacks are the loss of one equivalent of chiral alcohol and the difficulty of handling small quantities of PCl_3 due to volatility and moisture sensitivity. Furthermore, the method is restricted to alcohols (*vide infra*).
Under an inert atmosphere (N_2) phosphonate formation appears to be much slower and *Welch*[92] has shown that the enantiomeric excess of a number of chiral, secondary alcohols can also be determined from the ^{31}P NMR absorptions of the trialkylphosphites **102** initially obtained

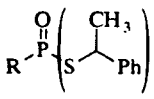


Scheme 30.



Scheme 31.

Table XII ^{31}*P-NMR data of the diastereomeric shift differences of* ***103–105*** *as a function of the substituent R, using α-methylbenzenemethanethiol.*



R substituent	Δδ (Hz) [a]
CH_3	109.30
$C_6H_5CH_2$	24.19
C_6H_5	7.38
$C_6H_5CH_2S$	12.33

[a] Absolute values between the D,L pair and respective *meso* diastereomers.

Table XIII ^{31}*P-NMR data for diastereomeric phosphonates* ***103, 104*** *and* ***105*** *(X = S, R = CH_3), recorded in $CDCl_3$; 0.1 M.*

D,L-Thiol	Δδ (Hz)		
	δ(*meso*)	δ(*meso*)	δ(D,L)
sulfanylaceticacidester	4660	4987	4725
α-methylbenzénemethanethiol	4523	4935	4632
thiomenthol	4640	4707	4694
tetrahydrofurane-3-methanethiol	5129	5088	5050
α-ethylbenzeneethanethiol	4940	4977	4954
N,N-dimethylsulfanylacetamide	4883	5088	5010

from PCl_3 and three equivalents of the chiral alcohol. A typical example is α-ethylbenzenemethanol **101** (Scheme 30).

Quartets are observed at δ 140.7 and δ 142.7 ppm in a statistical ratio of 3:1 for the *RRR* (*SSS*) isomers and the *RRS* (*SRR*) isomers of the phosphites, respectively. In the case of enantiomerically pure *R* (or *S*) alcohol only the signal belonging to the *RRR* (or *SSS*) isomer was observed at δ 142.7 ppm.

The enantiomeric excess is calculated from % *ee* = (2*a* − 1) · 100, were *a* is the molar fraction of one isomer which is related to the signal integral ratio *Q* by $Q = 3 \cdot a \cdot (1 - a)$.

In cases where the subsequent Arbuzov rearrangement can be sufficiently retarded by using 3 equivalents of base, this method is complementary to the phosphonate procedure although sofar it seems to be of rather limited use.

III.B $CH_3P(=O)Cl_2$ method[93]

Extension of the PCl_3 method to the *ee* determination of chiral thiols was not possible because thio-trialkylphosphites are obtained from PCl_3 and thiols instead of phosphonodithioates and the former do not give well resolved ^{31}P NMR signals for the diastereomers.

As there was no general method available for the *ee* determination of chiral thiols we were pleased to find that alkylphosphonic dichlorides **95** are highly suitable for this purpose (Scheme 31).

Alkylphosphonic dichlorides **95**[94] are very reactive towards thiols leading to quantitative formation of one D,L-pair, (*S,S*) and (*R,R*)-**103**, and two *meso* adducts **104** and **105** (X = S) in a few minutes. Reagent **95** can also be used as an alternative to PCl_3 for the *ee* determination of alcohols (Scheme 31, X = O), in particular acid sensitive ones, as excess base can be used to remove efficiently the liberated HCl[95].

The largest chemical shift differences for the diastereomeric products of **95** are obtained with methylphosphonic dichloride (**95**, R = CH_3). Increase of the size of the alkyl substituent R leads to a decrease in chemical shift dispersion Δδ, as is shown for α-methylbenzenemethanethiol derivatives (Table XII)[96].

Diastereomeric chemical shift dispersion for adducts of **95** (R = CH_3, X = S) compare favourably with adducts of other chiral derivatizing agents in the case of D,L-α-methylbenzenemethanethiol. Diastereomeric shift differences for the *meso* isomers and D,L pair of Δδ 1.35 and Δδ 3.74 ppm were observed whereas *Mosher*'s reagent[33] showed a difference of only Δδ 0.06 ppm (^{19}F NMR, Figure 6) and *Pirkle*'s reagent[15–18] resulted in a maximum separation of Δδ 0.05 ppm in the ^{1}H NMR spectrum.

The scope and limitations of $CH_3P(=O)Cl_2$ as a reagent for chiral thiols are illustrated in Table XIII.

It can be seen that the method is broadly applicable including aliphatic and secondary benzylic thiols, α-sulfanyl carboxylic esters and α-sulfanyl amides. In the few examples that no baseline separation is observed using $CDCl_3$ as solvent, recording of the ^{31}P NMR spectrum in the more polar CD_3OD results in (nearly) baseline separated signals. In addition a large increase of the diastereomeric shift dispersion is observed at lower temperatures. This temperature effect is particular advantageous in case the absorptions of *meso* **104** and **105** and D,L-**103** are not completely separated at room temperature; the effect widens the applicability of the method. Again, only small deviations from the statistical ratio of 50:50 for *meso* and D,L isomers are found[87,97].

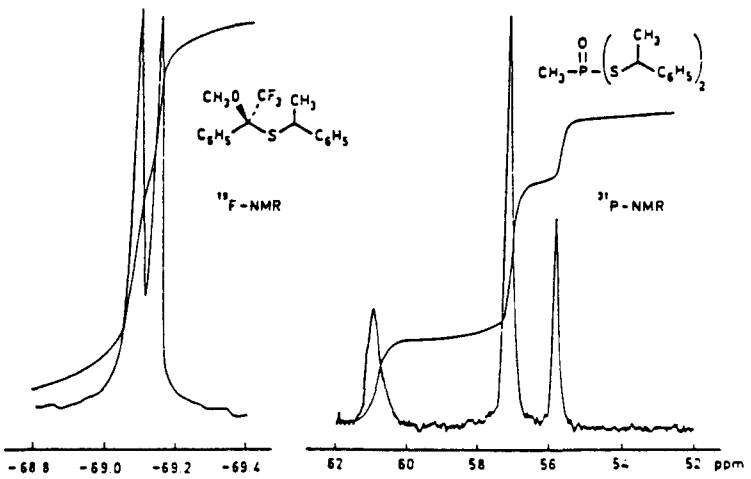
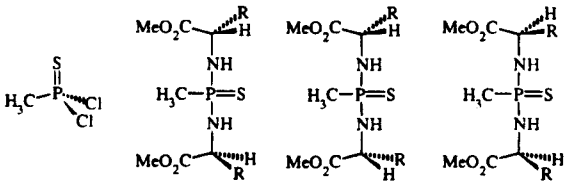


Figure 6. Comparison of peak separations for derivatives of α-methylbenzenemethanethiol using Mosher's reagent (a, ^{19}*F-NMR) and* ***95*** *(b,* ^{31}*P-NMR).*



96 106 (only SS shown) 107 (RS meso-1) 108 (RS meso-2)

Scheme 32.

Although extensive investigations revealed that $CH_3P(=O)Cl_2$ was not a satisfactory reagent for the derivatization of chiral amines[98], recent research of *Fedin* and co-workers[99] showed that the diastereomeric shift differences, *the self-induced diastereomeric anisochronity*, may be enhanced provided the measurements are performed in toluene at low temperature (−20°C). Probably, hydrogen bonding between the phosphoryl and amide moiety lies at the basis of these observations.

III.C $CH_3P(=S)Cl_2$ method[100]

It became clear that neither PCl_3 nor $CH_3P(=O)Cl_2$ is a satisfactory reagent for the derivatization of chiral amines (*vide supra*). Fortunately, alkylphosphonothioic dichlorides [$RP(=S)Cl_2$] are relatively stable, resistant to hydrolysis and provide in good yields the alkylphosphonothioic diamides upon treatment with amines[101,102]. Reagent **96** (R = CH_3) reacts in the presence of triethylamine quantitatively in a few minutes at −20°C with two equivalents of α-allylglycine methylester (R = allyl) to afford diastereomeric methylphosphonic diamides **106, 107** and **108** (Scheme 32).

The decoupled ^{31}P NMR spectrum shows three nicely separated singlets for the two *meso* compounds *RS*[1]-**107** and *RS*[2]-**108** and the racemic (*RR* and *SS*)-**106** adducts, with a *meso*/D,L ratio (49/51) virtually identical with theory (Figure 7).

The scope of this method encompasses a variety of primary amines and amino acid esters including sterically hindered ones. Representative examples are given in Table XIV.

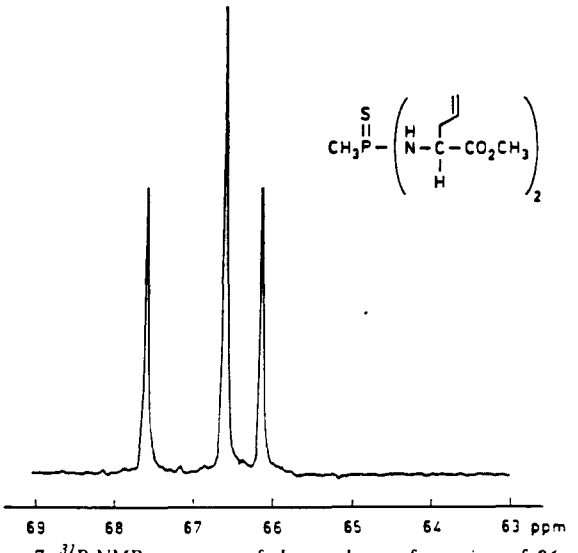


*Figure 7. ^{31}P-NMR spectrum of the products of reaction of **96** and racemic α-allylglycine methyl ester recorded in $CDCl_3$; 0.01 M.*

*Table XIV ^{31}P-NMR data of diastereomeric methylphosphonic diamides **106–108** recorded in $CDCl_3$; 0.1 M.*

D,L-Amine	δδ (Hz)		
	δ(*meso*)	δ(*meso*)	δ(D,L)
butan-2-amine	4995	5035	5015
phenylalanine	5507	5404	5395
α-methylmethionine	5504	5575	5485
α-allylglycine	5355	5472	5393
α-methylbenzenemethanamine	5086	5208	5168

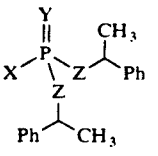
It should be noted that alkylphosphonothioic dichlorides are not satisfactory for the analysis of chiral secondary or tertiary amines. However, chiral diamine **109**, which is a typical example of a bifunctional compound containing both a primary and a tertiary amine center, readily forms the diastereomeric phosphonothioic diamide **110**, which shows well separated absorptions in the decoupled ^{31}P NMR spectra, allowing accurate *ee* determination[103] (Scheme 33).

The commercially available $C_6H_5P(=S)Cl_2$ can be used although $CH_3P(=S)Cl_2$, with a small alkyl substituent, is preferred because it gives superior diastereomeric chemical shift dispersions (see also *III.B*). Again, as with the use of thiols, a strong temperature dependency is observed, resulting in an approximately 1.5 fold increase of the diastereomeric shift dispersion at −20°C.

Examination of the currently available methods for the *ee* determination of chiral amines leads to the conclusion that the $CH_3(P=S)Cl_2$ method compares favourably in view of the large shift differences obtained for the diastereomers, the simple experimental procedure (no workup is required) and the ready availability of this achiral reagent.

A disadvantage of this method is that hydroxy amines or α-hydroxyamino acid derivatives (unless hydroxy protected) cannot be analyzed by this technique, due to severe side product formation.

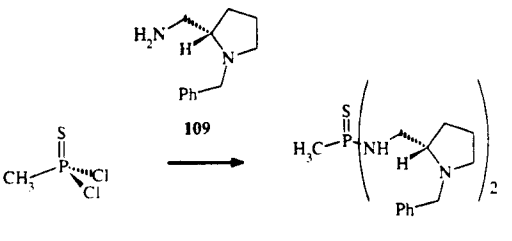
Information on the structural requirements for efficient derivatizing reagents was obtained by comparing a number of reagents **111** with a variety of *X*, *Y* and *Z* around phosphorus. Typical data are summarized in Tables XII, XIII and XIV.



111

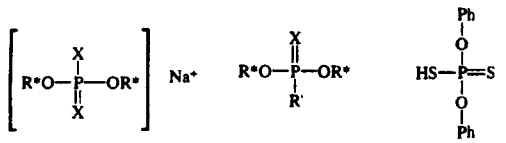
A number of important observations can be made:

(*i*) It appears that the largest chemical shift dispersion is found when X = H or a small alkyl group. This arrangement is also synthetically easier to achieve.



96 **109** **110**

Scheme 33.



112 X= O
113 X= S

114
X = O, S R' = H, alkyl

115

Scheme 34.

(*ii*) Thioderivatives (Y = S) give in general superior shift differences, except for these cases were Z = S.
(*iii*) Smaller $\Delta\delta$ values are found in the order X = OR < X = SR for diastereomeric (thio)phosphonates.
(*iv*) On comparison of chiral amines, thiols and alcohols the following order of diastereomeric shift dispersion is found: Z = NH > Z = S > Z = O.
(*v*) The chemical shift behavior of the diastereomeric products is very sensitive to solvent polarity effects and temperature of the measurements[35].

These observations are in accordance with the results using chiral phosphorus derivatizing agents (*vide supra*).

IV Related methodology

IV.A Phosphorus based methods

The ^{31}P NMR nonequivalence of diastereomeric dialkyl phosphorodithioates **113** (X = S) has also been used for the enantiomeric excess determination of chiral alcohols[104].

When *Horeau*'s principle (*vide supra*) is applied to (thio)phosphonates **114** (X = O, S; R^1 = H, alkyl) or (thio)phosphates **112** (X = O) or **113** (X = S), there is a distinct stereochemical difference (Scheme 34).

In the case of phosphonates **114**, derived from racemic alcohols, a D,L-pair and two *meso* isomers are formed whereas in (thio)phosphates **112** and **113** the phosphorus atom is stereogenic but achirotopic[87] resulting in a D,L-pair and one *meso* isomer only. As an achiral reagent $(C_6H_5O)_2P(=S)SH$ (**115**, Scheme 34) was used. Reaction of **115** with D,L-butan-2-ol gives diastereomeric di-*sec*-butyl phosphorodithioates **116** and **117** (Scheme 35).

In the ^{31}P NMR spectrum a singlet is observed for **116** obtained from enantiomerically pure *l*-butan-2-ol, whereas two singlets in a 50:50 ratio, for D,L-**116** and *meso*-**117**, are found using D,L-butan-2-ol (Figure 8). Again, ^{31}P-NMR nonequivalence of the diastereomeric (D,L and *meso*) phosphorodithioates allow *ee* determination of chiral alcohols. It should be emphasized that chiral phosphates (**112**, X = O) generally show only one (broad) absorption. It was also shown that it was possible to discriminate between *meso*- and D,L-phosphorodithioic acids using chiral tertiary amines (see Figure 8).

It is remarkable that despite the high symmetry at phosphorus in **113** when racemic alcohols are used diastereomeric nonequivalence is found in the decoupled ^{31}P NMR spectrum. The fact that only two singlets are observed is an advantage compared to derivatives **114**, although the diastereomeric shift differences are generally smaller, making them less suitable for practical application. The conversion of chiral alcohols into diastereomeric phosphonates can also be used for assessment of the enantiomeric composition by means of achiral HPLC[105].

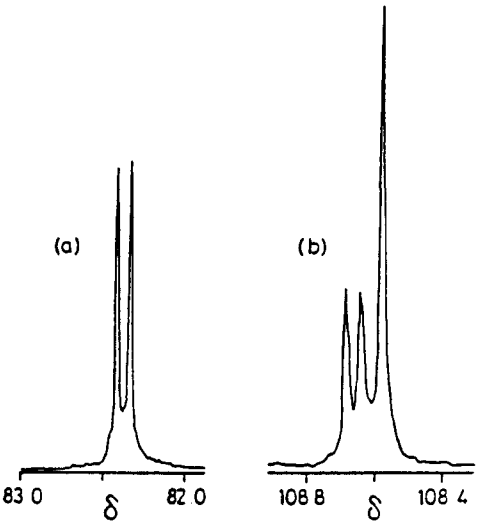


Figure 8. ^{31}P-NMR spectra of (a) 112 derived from racemic butan-2-ol; (b) (−)-cinchonidine salt of racemic 113 from butan-2-ol.

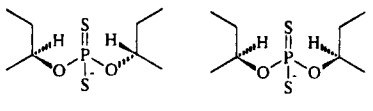
IV.B Non-phosphorus based methods: A comparison

Horeau demonstrated the intrinsic differences in chirality of an enantiomerically pure and racemic compound using dichlorides as achiral coupling agents for alcohols and showed the possibility to examine the enantiomeric composition by means of ^1H NMR and chromatographic techniques (see eqns. 1 and 2).

Recently an efficient method for *ee* determination of chiral alcohols by means of GC of dialkoxysilanes **118** was developed based on this principle using dialkylsilyl dichloride as a coupling reagent[106] (Scheme 36).

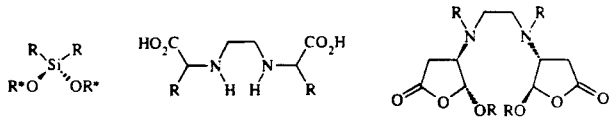
Pertinent examples are furthermore *N,N'*-ethylene-bridged amino acid dimers **119**[107] and the *N,N'*-bis(γ-alkoxybutyrolactone)-substituted diamines **120**[108]. In all cases the *Horeau* principle applies, although complicated spectra are often seen and these systems in general have not resulted in an effective methodology for *ee* determination.

Co^{III}-porphyrines **121** proved to be useful as NMR shift reagents due to their complexing power for instance with amines[109], as well as the fact that the cobalt-porphyrin systems, unlike the naturally occurring porphyrins, do not possess planar chirality. These Co^{III}-systems can form complexes with two nitrogen ligands in the axial positions, and these features make it possible, owing to the slow



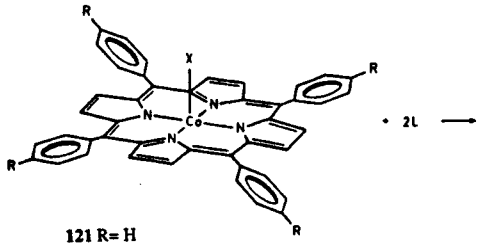
116 racemate (SS shown)
117 meso

Scheme 35.

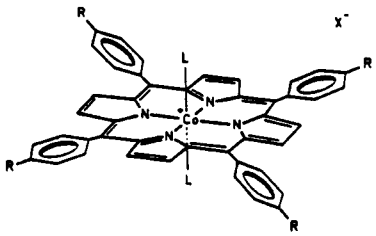


118
119
120

Scheme 36.



121 R= H
124 R= SO_3H



122 R= H
125 R= SO_3H

Scheme 37.

ligand exchange on the NMR time scale in the six-coordinate complex, to observe both diastereomeric complexes (*RR*, *SS* and *RS*) in the ^{1}H NMR spectrum provided that a racemic amine is used (Scheme 37).

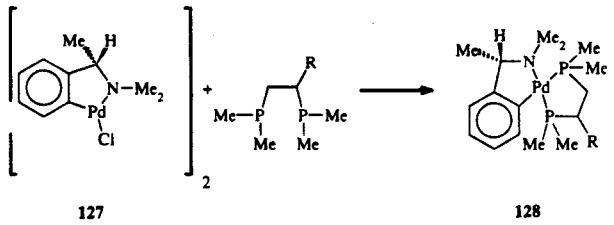
Complex **122** with *R* (or *S*) amines is optically active and exhibits planar chirality through the porphyrin ring plane, whereas the *meso R,S*-adduct **123** (not shown) is optically inactive due to the pseudo-chirality or pseudo-asymmetry about the porphyrin ring plane[110]. *Abraham* and coworkers[111] were able to determine the enantiomeric composition of α-methylbenzenemethanamine and levamisole in $CHCl_3$. Although the chemical shifts are usually very large (in the order of several ppm's), the diastereomeric shift differences ($\Delta\Delta\delta$ values of about 0.005 ppm are observed) are only significant when high field strengths are applied. This method can also be applied to chiral amino alcohols.

Recently, a water-soluble Co^{III}-shift reagent was developed based upon *meso*-tetrakis-(4-sulfonatophenyl)porphyrin **124**. Following *Horeau*'s principle complexation of two amino acids (or derivatives) to Co^{III}-**124** allows *ee* determination of these compounds even in polar solvents like water or water/alcohol mixtures[112]. Typical examples are summarized in Table XV.

Sufficient resolution is seen in particular with α-alkylated amino acids. Shifts are, however, strongly variable depending on the pH and solubility of the Co^{III}-substrate complexes D,L-**125** and *meso*-**126** (not shown). Only those substrates that give simple resonances (at least for some protons) in the ^{1}H NMR spectrum provide enough resolution to allow accurate analysis. The attempted use of ^{59}Co NMR as an alternative technique was not successful.

*Table XV ^{1}H-NMR $\Delta\Delta\delta$ values of complexes **125** and **126** using racemic amino acids, recorded in D_2O / Na_2CO_3 (nucleus of interest).*

D,L-Amino acid	$\Delta\Delta\delta$ (ppm)
alanine	0.06 (β)
phenylglycine	0.02 (β)
phenylalanine	0.08 (β)
α-vinylalanine	0.12 (β)
α-phenylalanine	0.11 (β)



127 128

Scheme 38.

V Enantiomeric excess (*ee*) determination of phosphorus compounds

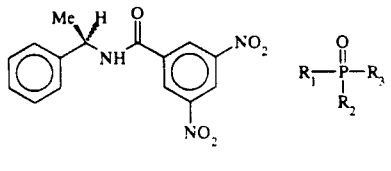
When phosphorus containing reagents are used for the *ee* determination it is of great importance to have access to *ee* determining methods for this type of materials. The methods described (*vide supra*) can in principle[113] also be used to determine the *ee* of the phosphorus derivatizing reagents by using enantiomerically pure substrates and the partially racemic phosphorus materials. There are, however, few methods known especially developed to determine the enantiomeric composition of chiral phosphorus compounds. The enantiomeric composition of chiral, chelating diphosphines can be determined by means of *in situ* derivatization with (−)-bis(μ-chloro)bis[(*R*)-dimethyl(α-methylbenzyl)-aminato-C^2, *N*]dipalladium(II) **127**[114] (Scheme 38).

Upon dissolving 1 equivalent **127** and 2 equivalents chiral diphosphine in $CDCl_3$, diastereomeric adducts **128** are formed, which are analyzed by means of ^{1}H or ^{31}P NMR. Although there is evidence for decoordination of one of the chelating phosphines to form a tricoordinate species, the method has proven to be applicable for several diphosphines, including (*R,R*)-2,2-dimethyl-4,5-bis[(diphenylphosphino)methyl]dioxalane DIOP. It has to be noted that, after the determination is done, the phosphines can be recovered essentially quantitatively, if desired.

Duñach and *Kagan*[115] were able to determine the enantiomeric composition of a variety of chiral phosphine oxides **130** by using (*R* or *S*)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzenemethanamine **129** as chiral shift reagent (Scheme 39).

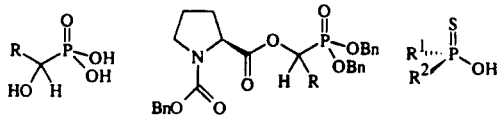
The procedure consists of mixing of equimolar amounts of shift reagent and phosphine oxide in $CDCl_3$ followed by analysis by means of ^{1}H NMR. The diastereomeric shift dispersion is relatively small, *i.e.* $\Delta\delta$ 7 Hz (when spin decoupling is used) for D,L-DIOP, which is transformed to the oxide *in situ* by treatment with ^{t}BuOOH just prior to determination. The enantiomeric composition of chiral (1-hydroxyalkyl)phosphonic acids **131** can be determined by means of derivatization into diastereomeric phosphonodidepsipeptides **132**, which can be analyzed using ^{31}P NMR[116] (Scheme 40).

The derivatization method consists of a coupling of the 1-hydroxyalkylphosphonic acids **131** with *N*-protected L-



129 130

Scheme 39.



131 132 133

Scheme 40.

amino acids using DCC to facilitate the coupling. The obtained phosphonodidepsipeptides **132** are quantitatively distinguishable in the decoupled ^{31}P NMR. The values of the diastereomeric shift dispersions differ with the change of the L-amino acids and the protecting groups, and range from $\Delta\delta$ 0.06 to 0.60 ppm. The method is performed readily, since *e.g.* Boc-L-Val and Boc-L-Phe are commercially available.

Another method for the *ee* determination of (1-hydroxyalkyl)phosphonic acids **131** is based upon the formation of diastereomeric salts using α-methylnaphthalene-1-methanamine **5** (R = H) as chiral auxiliary[117] in nonpolar solvents like $CDCl_3$[118].

Although the magnitude of the diastereomeric shift dispersion is sensitive to concentration, temperature and (enantio)-purity of the phosphonates and the amine[119], the magnetic nonequivalence is large enough to allow proper quantification, *i.e.* for monobenzyl ester phosphonate salts $\Delta\delta$ values of 0.36 ppm are obtained.

The *ee* of chiral phosphorus thio acids **133** (Scheme 40) can be determined by means of diastereomeric salt formation using optically active amines such as **5** (R = H)[120]. The salts show diastereomeric nonequivalences in the ^1H, ^{13}C and ^{31}P NMR spectra, provided that these are taken in nonpolar solvents (*vide supra*). The diastereomeric shift dispersions are sensitive to several factors, and are generally small but distinct, *i.e.* between the $\Delta\Delta\delta$ 0.6 and 18.6 Hz (^1H NMR) for phosphorus thio acids **133** (R^1 = Me, R^2 = OMe) and **133** (R^1 = Me, R^2 = BuO), respectively, using (*S*)-α-methylbenzenemethamine. Since the ^1H NMR spectra tend to be complex due to P–H and H–H coupling, ^{31}P NMR proved to be an alternative since these provide only two signals for (partially) racemic phosphorus thio acids. Moreover, the two techniques appeared to be complementary as is shown for phosphorus thio acid **133** (R^1 = Ph, R^2 = Me), which shows a $\Delta\Delta\delta$ value of 14.4 Hz in the ^1H-NMR and no separation in the ^{31}P-NMR using (*S*)-α-methylbenzenemethanamine whereas for **133** (R^1 = Ph, R^2 = *t*-Bu) no separation was found in the ^1H NMR but $\Delta\Delta\delta$ 24.4 Hz in the ^{31}P NMR using *S*)-α-methyl naphthalene-1-methamine. It is interesting to note that nonequivalences were also observed in the case the chirality on phosphorus was introduced by isotopic exchange (*D* for *H*) as is shown for **133** ($R^1 = CH_3$, $R^2 = CD_3$). Despite the slight differences between these groups, a remarkable $\Delta\Delta\delta$ value of 4.1 Hz was observed in the ^1H NMR! At this point it should be noted that the diastereomeric shift dispersion is also visible in the ^{13}C NMR, although the prolonged time to record a ^{13}C spectrum that also contains excessive P–C coupling is clearly less attractive. Furthermore, this particular article provides a very detailed study concerning the chirality aspects of diastereomeric salt formation[120].

Diastereomeric salt formation can also serve as a tool to follow the resolution on a continuous manner as has been shown by *Kuchen* and *Kutter*[121]. They were able to resolve (4-methoxyphenyl)methylphosphinothioc acid by means of crystallization of the diastereomers using optically active quinine and use the same combination to determine the enantiomeric composition of the mixture at any moment by means of ^{31}P-NMR, for which a $\Delta\Delta\delta$ value of 0.3 ppm were observed.

We were able to use diastereomeric salt formation as method for the *ee* determination of phosphoric acids **41**[122] (Scheme 13), employing enantiomerically pure amines or amino alcohols like *e.g.* L-ephedrine (Figure 9).

Surprisingly, the method is not applicable for the determination of the *ee* of the amines or amino alcohols (the reciprocal situation), by using enantiomerically pure phosphoric acid. This clearly shows that great care has to be taken when dynamic systems are used for *ee* determining processes.

Self-association of enantiomers, *i.e.* of chiral phosphonates or phosphonic amides in solution, would result in diastereomeric aggregates which in principle allow *ee* determination by ^{31}P NMR, following the principle introduced by *Horeau* (*vide supra*).

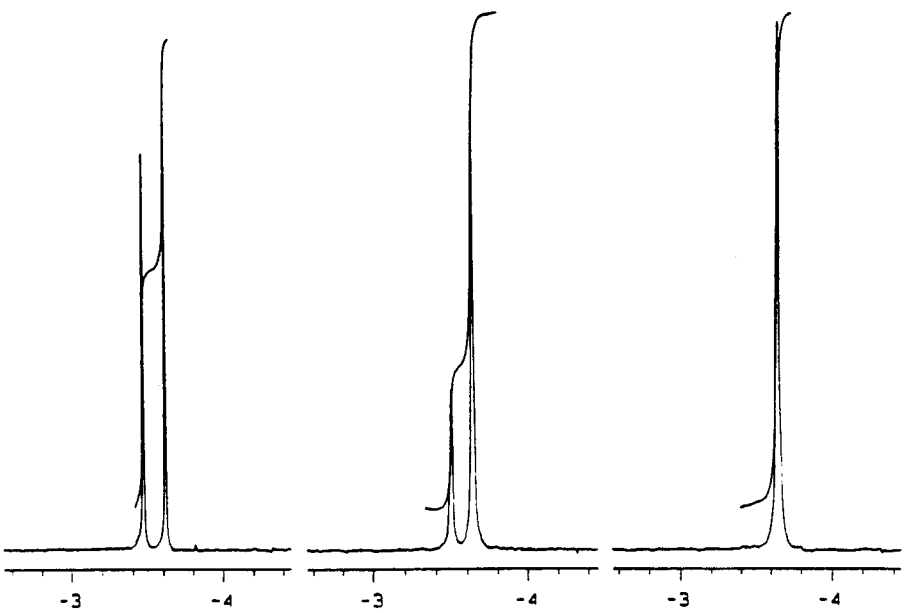
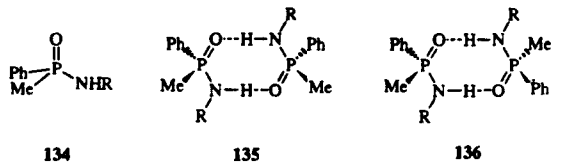
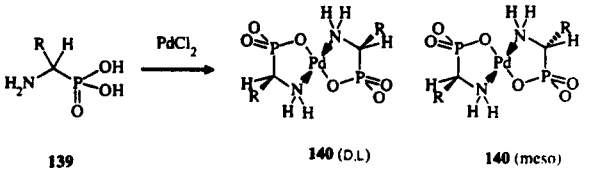


Figure 9. ^{31}P-NMR spectra of L*-ephedrine with: (a) racemic* ***41*** *(R = 2-Cl); (b) (−)-****41*** *(R = 2-Cl) 45% ee and (c) (−)-****41*** *(R = 2-Cl) 98% ee.*



134 135 136

Scheme 41.



139 140 (D,L) 140 (meso)

Scheme 43.

Harger[123] has demonstrated the ^{1}H NMR nonequivalence of amide **134** (and several analogues), which exhibits two distinct doublets (due to a phosphorus coupling) for the methyl groups whereas enantiomerically pure **134** and racemic **134** show a single doublet signal (Scheme 41).

The observed NMR nonequivalences can be rationalized via molecular association involving H-bonding to yield diastereomeric complexes **135** and **136**. This allows *ee* determination of this type of chiral phosphorus compounds based on self-recognition, although the applicability seems to be limited to special cases so far. Also combinations of amides and phosphonates can be analyzed.

Pasquier and *Marty* were able to determine the enantiomeric composition of 1-(diphenylphosphino)propane-2-thiol (**137**) by the addition of less than one equivalent of $Ni(NO_3)_2 \cdot 6H_2O$ in CH_2Cl_2/MeOH (10/1)[124]. By complexation of two molecules of **137** to Ni^{II} the *meso* and D,L diastereomers of *trans*-Ni^{II} **138** are formed *in situ* (Scheme 42), which can be analyzed by means of ^{31}P NMR, showing two nicely separated singlets with a diastereomeric shift dispersion of $\Delta\delta$ 0.80 ppm.

A further example using this methodology is the chelation of two molecules of chiral (1-aminoalkyl)phosphonic acid **139** with Pd^{II} in alkaline D_2O solutions[125]. The obtained diastereomers, the optically active *R,R* (or *S,S*) and *meso* (*R,S*) forms **140** (Scheme 43), give diastereomeric shift differences up to $\Delta\delta$ 0.18 ppm, depending on the structure of the phosphonic acid used.

Another remarkable example, where the substrate serves as its own reference, is by making use of the different crystallization behaviour of enantiomers and (partially) racemates which can be detected by using ^{31}P solid-state magic-angle spinning NMR (^{31}P MAS NMR)[126]. The enantiomers and racemates generally crystallize in different point groups, and crystallization of a mixture of two enantiomers gives some racemic crystallite the amount of which is governed by the quantity of the enantiomer representing the minor constituent.

VI Conclusions

Due to the increasing number of phosphorus derivatizing reagents and the ready availability of NMR spectrometers able to record phosphorus spectra on a routine basis, phosphorus NMR rapidly gained importance in the field of *ee* determination. The high sensitivity and abundancy of the phosphorus nucleus and the relatively simple spectra of the diastereomeric products if broad-band ^{1}H-decoupling is used, clearly indicate the advantages. Moreover, phosphorus derivatizing reagents are very reactive towards a large number of substrates, including alcohols, amines, thiols, amino alcohols and amino acids. Also chiral alkenes and sulfoxides can be analyzed using phosphorus-based methods. The high reactivity is sometimes, however, a disadvantage since the application of these reagents require drastic exclusion of *e.g.* water and/or air.

Alternatively, chiral phosphorus reagents designed to be used in aqueous solutions have been successfully applied. Although in the past many phosphorus derivatizing reagents were based on expensive chiral starting materials, several reagents are now available based on much cheaper auxiliaries and even very cheap achiral reagents, like PCl_3.

Our knowledge of steric and electronic factors of the phosphorus reagents influencing the diastereomeric shift dispersions is rapidly growing and several new or improved reagents can be foreseen to be developed in the near future.

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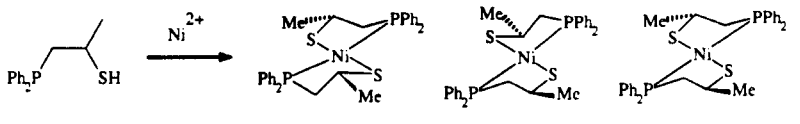

137 138

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